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COMPREHENSIVE REVIEW OF UROLOGY

directed by Aria F. Olumi, MD

BETH ISRAEL DEACONESS MEDICAL CENTER

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Comprehensive Review of Urology

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Oakstone Publishing, LLC

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TARGET AUDIENCE:

The activity was designed to provide urologists, urology fellows and residents, surgery residents interested in urology, other licensed individual practitioners or ancillary staff interested in urology, or who participate in the delivery of urologic care with current, relevant, and condensed information needed to pass certification and recertification exams.

ESTIMATED TIME TO COMPLETE:

It is estimated that it should take the average learner **56** hours to complete the activity.

ACCREDITATION:

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Contact Hours: 56

SPECIAL PREREQUISITES FOR PARTICIPANTS: There are no prerequisites for participants.

METHOD OF PARTICIPATION: Review Video/Audio program, score 70% or greater on the required posttest to assess the knowledge gained from reviewing the program and complete the comprehensive activity evaluation.

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LEARNING OBJECTIVES:

At the conclusion of this activity, the participant will be able to:

- Discuss the discrete urologic infections and inflammatory disorders and how they are best managed.
- Describe the best surgical approaches for urologic trauma.
- Identify the ideal treatment approaches for patients with kidney cancer.
- Differentiate between non-muscle invasive bladder cancer and muscle invasive bladder cancer.
- Summarize the most efficacious therapies for bladder cancer.
- Differentiate between medical approaches and surgical approaches for prostate cancer.
- Describe active surveillance in prostate cancer.
- Assess the importance of adolescent and transitional urology.
- List common and uncommon urologic conditions in children.
- Define male and female sexual dysfunction.
- Explain evaluation and medical and behavioral management of urinary incontinence in women.
- Distinguish among the benefits of medical and surgical management of lithiasis.

FACULTY AFFILIATIONS DISCLOSURE:

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Topic/Speaker	Book Page #
GENERAL	
Radiologic Evaluation of Renal Masses <i>Steven Raman, MD</i>	1
Imaging for Advanced Metastatic Cancer <i>Mukesh Harisinghani, MD</i>	28
Prostate MRI for Evaluation of Prostate Cancer: An Overview of Techniques and Interpretation <i>Leo L. Tsai, MD, PhD, MSc</i>	37
Scrotal Ultrasound <i>Aoife Kilcoyne, MD</i>	41
Pathology of the Prostate, Kidney, and Adrenals <i>Chin-Lee Wu, MD</i>	46
Pathology of the Bladder <i>Justine A. Barletta, MD</i>	66
Pathology of the Testis <i>Robert H. Young, MD, FRCPath</i>	79
Pathology of the Penis <i>Robert H. Young, MD, FRCPath</i>	96
Urologic Emergencies <i>Jay Simhan, MD, FACS</i>	102
Laser Physics and Safety <i>Lori Lerner, MD</i>	116
INFECTIOUS AND INFLAMMATORY DISEASE	
Infections of the Urinary Tract <i>Elise J. B. De, MD</i>	129
Minimizing Risks Associated with Catheter-Associated Urinary Tract Infections (CAUTI) <i>Lona Mody, MD, MSc</i>	139
Interstitial Cystitis <i>Christopher K. Payne, MD</i>	146
Chronic Pelvic Pain in Men <i>Jeannette M. Potts, MD</i>	160
INFERTILITY AND SEXUAL DYSFUNCTION	
Male Infertility <i>Cigdem Tanrikut, MD</i>	172
Erectile Dysfunction <i>Arthur L. Burnett, MD, MBA</i>	184
Peyronie Disease and Priapism <i>Hossein Sadeqhi-Nejad, MD, FACS</i>	191

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Comprehensive Review of Urology

Topic/Speaker	Book Page #
INFERTILITY AND SEXUAL DYSFUNCTION	
Female Sexual Health <i>Leah S. Millheiser, MD</i>	210
Transgender – Male to Female Surgery <i>Robert D. Oates, MD</i>	219
MALE GENITALIA	
Cancer of the Testis <i>Joel Sheinfeld, MD</i>	228
Penile Cancer <i>Curtis A. Pettaway, MD</i>	257
Urethral Cancer <i>Curtis A. Pettaway, MD</i>	268
Disorders of the Scrotum and Seminal Vesicles <i>Jay I. Sandlow, MD</i>	279
TRAUMA	
Renal and Upper Urinary Tract Trauma <i>Jay Simhan, MD, FACS</i>	290
Bladder and Prostate Trauma <i>Richard Santucci, MD</i>	306
Urethral Trauma <i>Thomas G. Smith III, MD, FACS</i>	313
Genital Trauma <i>Lee C. Zhao, MD, MS</i>	320
URINARY OBSTRUCTION AND NEPHROLITHIASIS	
Urinary Tract Obstruction <i>Stephen Y. Nakada, MD, FACS</i>	331
Urinary Lithiasis – Medical Management <i>David S. Goldfarb, MD</i>	340
Urinary Lithiasis – Surgical Management <i>Peter L. Steinberg, MD</i>	352
RENAL DISEASE	
Kidney Cancer – Active Surveillance <i>Adam S. Feldman, MD</i>	359
Kidney Cancer – Open Surgical Management <i>Christopher G. Wood, MD, FACS</i>	371

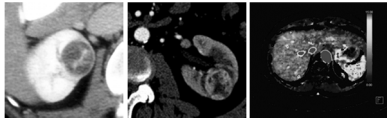
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Topic/Speaker	Book Page #
RENAL DISEASE	
Kidney Cancer – Laparoscopic Management <i>Andrew A. Wagner, MD</i>	393
Kidney Cancer – Systemic Therapy for Advanced Disease <i>David F. McDermott, MD</i>	404
Kidney Cancer – Ablative Therapy <i>Ruslan Korets, MD</i>	417
Acute Kidney Disorders <i>Melanie P. Hoenig, MD</i>	428
Chronic Kidney Disorders <i>David J.R. Steele, MD</i>	439
Cancer of the Renal Pelvis and Ureter <i>Vitaly Margulis, MD, FACS</i>	449
INCONTINENCE AND VOIDING DISORDERS	
Urinary Incontinence in Women: Evaluation and Medical Management <i>Gary E. Lemack, MD</i>	458
Surgical Management of Stress Incontinence in Women <i>Toby C. Chai, MD</i>	472
Management of Sphincteric Urinary Incontinence After Radical Prostatectomy <i>Craig V. Comiter, MD</i>	482
Urinary Tract Fistula <i>Elise J.B. De, MD</i>	493
BLADDER	
Bladder and Urethral Diverticula <i>Eric S. Rovner, MD</i>	520
Non-Muscle Invasive Bladder Cancer <i>Angela B. Smith, MD, MS, FACS</i>	531
Intravesical Therapy for Management of Non-Muscle Invasive Bladder Cancer <i>Zachary L. Smith, MD</i>	544
Surgical Management of Muscle Invasive Bladder Cancer <i>Bernard H. Bochner, MD</i>	556
Bladder-Preserving Trimodality Therapy for Management of Muscle Invasive Bladder Cancer <i>Jason A. Efsthathiou, MD, PhD</i>	569
Advances in Systemic Therapy for Management of Muscle Invasive Bladder Cancer <i>Richard J.B. Lee, MD, PhD</i>	588
Urinary Diversion and Bladder Replacement <i>Siamak Daneshmand, MD</i>	603

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Comprehensive Review of Urology

Topic/Speaker	Book Page #
PROSTATE	
Benign Prostatic Hyperplasia – Medical Management <i>Steven A. Kaplan, MD</i>	619
Benign Prostatic Hyperplasia – Surgical Management <i>Lori Lerner, MD</i>	633
Prostate Cancer Screening <i>Kristen R. Scarpato, MD, MPH</i>	639
Prostate Cancer – Active Surveillance <i>Stacy Loeb, MD</i>	651
Prostate Cancer – Biomarkers <i>Todd Morgan, MD</i>	661
Prostate Cancer: Utilization of MRI for Screening, Diagnosis, and Management <i>Mohammad Minhaj Siddiqui, MD</i>	671
Prostate Cancer – Focal Therapy <i>Behfar Ehdaie, MD, MPH</i>	683
Prostate Cancer – Surgical Management <i>Gerald L. Andriole, MD</i>	689
Radiation for Prostate Cancer in the Definitive and Post-Operative Setting <i>Paul Nguyen, MD</i>	707
Patient-Reported Outcomes After Localized Prostate Cancer Treatments <i>Peter Chang, MD, MPH</i>	726
Systemic Therapy for Metastatic Prostate Cancer <i>Richard J.B. Lee, MD, PhD</i>	734
PEDIATRIC UROLOGY	
Perinatal Urology <i>Vijaya Vemulakonda, MD, JD</i>	745
Common Pediatric Urologic Conditions: Kidneys, Genital Tract <i>J. Todd Purves, MD, PhD</i>	758
Common Pediatric Urologic Conditions: Congenital Disorders, Bladder <i>Hillary Copp, MD, MS</i>	776
Pediatric Trauma <i>Michael P. Kurtz, MD</i>	788
Urologic and Renal Cancer in Children <i>Patricio C. Gargollo, MD</i>	807
Adolescent and Transitional Urology <i>Carlos R. Estrada, Jr., MD, MBA</i>	825

New Concepts in Imaging of Primary Renal Cancer: Can imaging predict histology and tumor microenvironment?



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Radiology

Disclosures

- No Relevant Disclosures



Radiology

Outline

- Overview of Renal Masses
- Cystic Renal Lesions
- Subtypes of Renal Cell Cancers
- Imaging of Renal Lesions
- Importance of Multiple Phases
- Solid Renal Masses
 - RCC subtypes
 - Benign lesions
- Imaging based prediction of RCC Biology



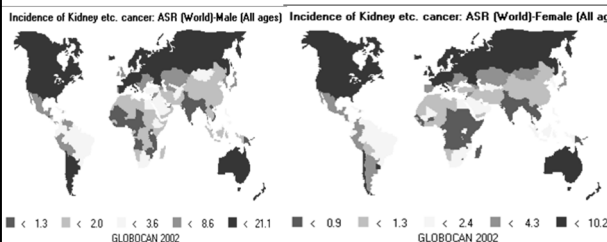
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Overview of Renal Cell Carcinoma



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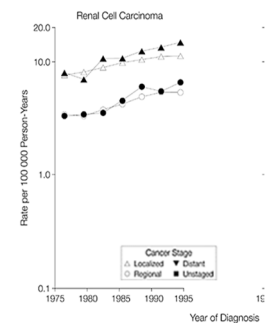
Renal Cell Carcinoma



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Renal Cell Carcinoma

- 2% increased incidence/year
- 125% increase last 30 years
- 70%: < 3 cm (T1a)
 - asymptomatic
 - 1960's: < 10% T1a
- Incidence
 - 330,000/yr
 - 65,000 cases/yr (US)



Chow, W.-H. et al. JAMA 1999;281:1628-1631.



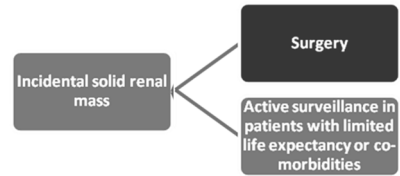
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All Solid Renal Masses Need to Come out, Right ?



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The Old Paradigm

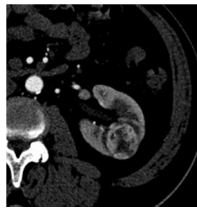


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Majority of Solid Renal Masses are cancers

Frank et al. J Urol 2003

- > 2770 solid renal masses
- Benign lesions:
 - 25% < 3 cm
 - 30% < 2 cm
 - 44% < 1 cm



- Lipid poor AML
- Oncocytoma

Tuncali. Radiology 2004: 10/27 lesions: lipid poor AML
Gill et al. J Urol 2003: 27% of nephrectomies benign



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T1a Renal Masses Grow Slowly & Are Low Grade



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Growth Rate of Renal Masses

Reference	Year	N lesions in series	Mean (range)		Growth rate cm/year
			Size at presentation, cm	Duration of follow-up, months	
Oda et al. [18]	2003	16	2.0* (1.0-4.5)	25*	0.54* (0.1-1.35)
Kato et al. [17]	2004	18	1.98 (0.8-3.4)	27	0.42 (0.08-1.60)
Volpe et al. [14]	2004	32	2.48 (0.9-3.9)	35	0.1 (NA)
Kassouf et al. [13]	2004	26	2.37 (1.0-7.0)	32	0.09 (0-1.2)
Bosniak et al. [15]	1995	40	1.73 (0.2-3.5)	39	0.47 (0-1.1)
Wehle et al. [10]	2004	29	1.83 (0.4-3.5)	32	0.12 (NA)
Lamb et al. [12]	2004	36	7.2 (3.5-20.0)	28	0.39* (0-1.76)
Sowery et al. [11]	2004	22	4.08 (2.0-8.8)	26	0.86 (NA)
Fujimoto et al. [19]	1995	6	2.47 (1.8-3.4)	29	0.47 (0.05-0.73)
Chawla et al. [16]	2006	61	2.97 (1.0-12.0)	36	0.20 (-1.64, 1.80)
[16] meta-analysis	2006	234	2.60 (NA)	34	0.28 (NA)

*median; NA, not available. Reproduced from [16] and Uzzo [23].



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Relationship of Tumor Grade to Size

Small Renal Masses: SEER Data

Tumor Size	Low Grade (%)	High Grade (%)	Totals
< 4 cm	7729 (86)	1250 (14)	8979
4-7 cm	5015 (79)	1361 (21)	6376
> 7 cm	2439 (70)	1024 (30)	3463
Totals	15,183 (81)	3635 (19)	18,818

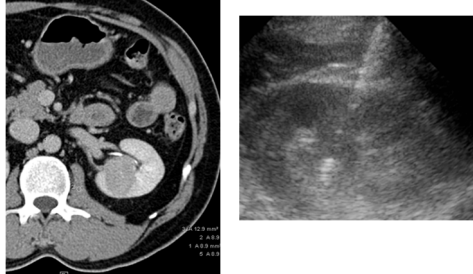
90% are Low Grade



Rothman, Uzzo et al J Urol 181: 2009

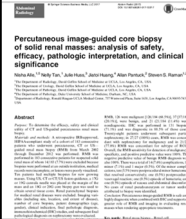
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Renal Mass Biopsy



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Biopsy of Renal Masses



- Excellent
- Use histology, immunostains, genetics
- Can use 18-25G needles for diagnosis
- UCLA series of > 180 patients:
 - 90% sensitivity; 100% specificity
 - 80% correlation with Gleason Grade
 - No significant complications



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Biopsy of Renal Masses

Established Indications for Perc Bx

- Patients with a renal mass and known extrarenal primary cancer
 - Resectable RCC vs mets
- Patients with a renal mass and imaging findings suggestive of unresectable renal cancer
- Patients with a renal mass and with comorbidities that increase risk of surgery
 - Heart and lung disease
 - Solitary kidney
 - Renal insufficiency
- Patients with a renal mass possibly caused by infection
 - Bacterial pyelonephritis can mimic renal tumor

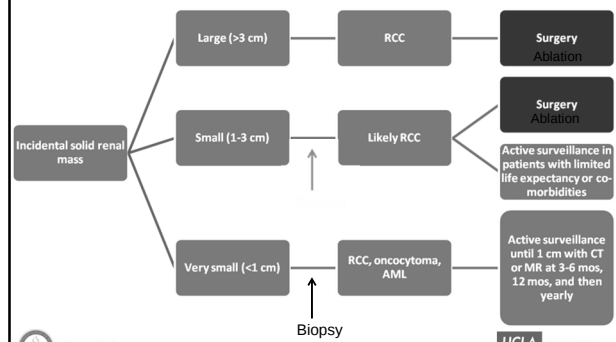
Emerging Indications for Perc Bx

- Patients with small (≤ 3 cm), hyperattenuating, homogeneously enhancing renal mass
 - E.g. benign tumors (lipid poor AML)
- Patients with a small renal mass (≤ 3 cm), for which percutaneous ablation is being considered
 - May avoid ablation if biopsy reveals a benign mass



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Algorithm 2018



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Cystic Renal Lesions



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Cysts

- Vastly more common than all other renal lesions
- Present in 50% of those > 50
- Should not be present in children
- Should not have > 2 cysts/kidney in 30's and 40's



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Complex Cysts

- Cysts may be complicated by hemorrhage, infection, ischemia
- Resulting in:
 - Septations
 - Calcifications
 - Internal debris
 - But not mural nodules



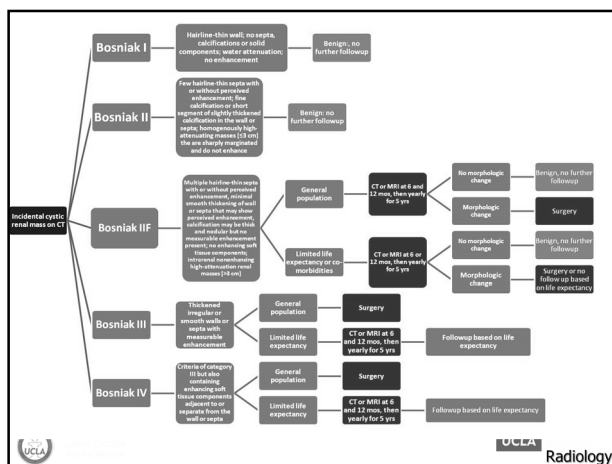
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Complex Cysts

- Bosniak Classification
 - CT or MR based stratification of cysts to assign a probability of malignancy
 - Bosniak I and II: non surgical
 - Bosniak III and IV: surgical due to 60 – 90% chance of malignancy



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Bosniak Category 1

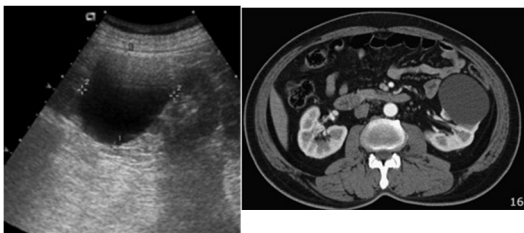
- simple benign cysts
- homogenous water attenuation, and a sharp interface with adjacent renal parenchyma (1/4 circumference open)
- no wall thickening, calcification, or enhancement.



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Bosniak I Cyst

- Simple cyst



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Bosniak Category II

- Likely benign cyst: (< 3 cm diameter)
- one or two thin (≤ 1 mm) septations or thin, fine calcification in their walls or septa
- hyperdense homogenous cysts
- one quarter of its wall extends outside the kidney
- nonenhancing after contrast material is administered.



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Bosniak II Cyst

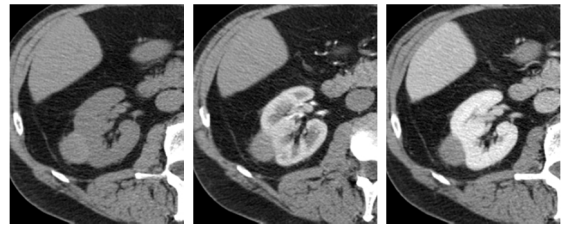
- Simple cyst plus
 - uniform high density
 - Multiple thin septations
 - Thin peripheral calcifications
 - Infected cysts



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Hemorrhagic cyst



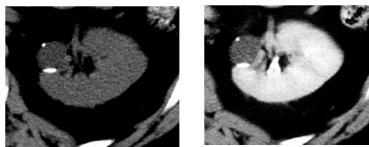
- Hemorrhagic cyst. No enhancement on any phase. HU range 44→49



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Bosniak II



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Bosniak Category IIc

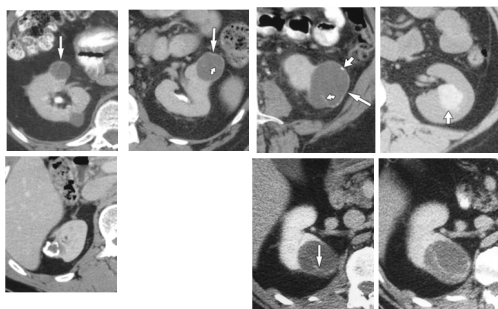
- These lesions have some suspicious features that deserve follow-up up to detect any change in character.
- All Type II lesions > 3 cm
- *Bosniak AJR 2003*: 2/42 lesions followed up were malignant



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Bosniak IIc Cystic lesions



Israel, G. M. et al. Am. J. Roentgenol. 2003;181:627-633



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Bosniak III Cyst

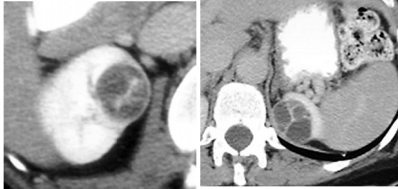
- High non uniform density
- Thick septa
- Nodularity without enhancement
- Thick calcifications
- Multiple loculations
- 50-60% are RCC



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Bosniak III



Hartman, D. S. et al. Radiographics 2004;24:



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Bosniak IV Cystic Lesion

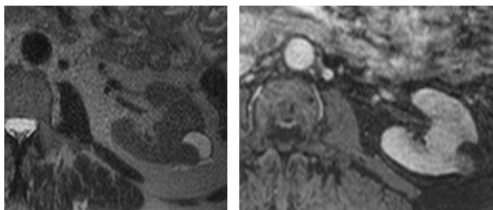
- Any of Class III features with solid enhancing tissue



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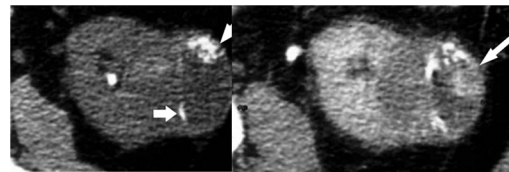
Bosniak IV Clear Cell RCC



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Radiology

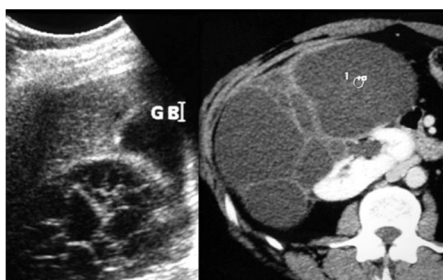
Bosniak IV



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Multilocular Cystic Nephroma



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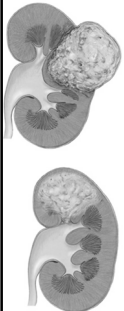
Radiology

Solid Renal Lesions: Balls vs Beans

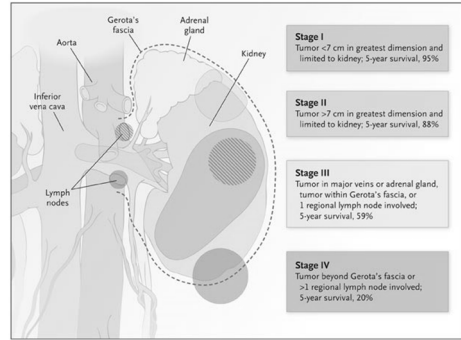
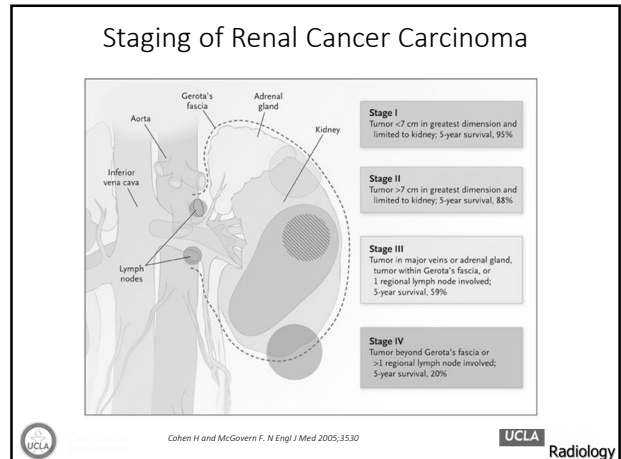


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- Balls
 - Expansile, well defined, spherical
 - Most renal lesions (RCC, AML, cysts, AVM)
- Beans
 - Reniform, ill defined, infiltrative
 - Infiltrating neoplasms (infiltr RCC, TCC)
 - Infections
 - Infarctions

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Cohen H and McGovern F. *N Engl J Med* 2005;3530

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Subtypes of Renal Cancer



UCLA Radiology

[illegible]

Three histological images of renal cell carcinoma subtypes: Clear cell, Papillary, and Chromophobe.

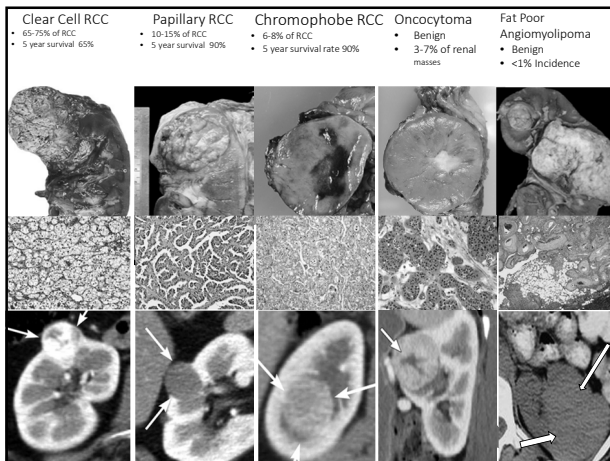
-

Oncocytoma	Fat-poor AML
------------	--------------

Radiology

[illegible]

iology

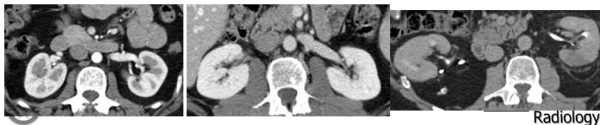


Imaging of Renal Lesions



UCLA CT Protocol for Renal Mass Detection and Follow up

- On 16-64 detector CT
 - Unenhanced scan
 - Enhanced scan phases:
 - Inject 100-150 cc Omnipaque 350 @ 3-4 cc/sec
 - Bolus tracking (image @ 25 sec after aorta HU > 150)
 - Corticomedullary phase scan (45 sec)
 - Nephrogenic phase scan (80-90 sec)
 - Excretory phase scan (3 min)



Radiology

UCLA MR Protocol for Renal Mass Detection and Follow up

- Axial & Coronal SSFSE/HASTE T2
- Axial multishot FSE/TSE T2
- Axial dual echo GRE T1
- Axial 2D or 3D GRE T1 w/ fat sat
- Dynamic 2D or 3D GRE T1 w/fat sat at 30, 60, 90, 120 & 180 sec after injection of 0.1mmol Gd @ 2cc/sec
- Subtraction imaging
- Diffusion (b 0, 50, 400, 800) / ADC
- Feraheme (4mg/kg)



Ultrasound

- Grayscale
- Color, Power and Spectral Doppler
- Microbubble Contrast
 - Definity 0.3 cc/injection with 10 cc saline flush
 - Lumason 2.4 cc/injection with 10cc saline flush



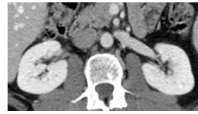
Corticomedullary Phase



- Contrast in cortical capillaries, peritubular spaces and proximal cortical tubular lumina
- Cortex enhances brightly, medulla not yet opacified
- Intense corticomedullary differentiation (>100 HU)



Uniform Nephrogram Phase



- Greatest yield for detection in this phase (84 more lesions < 3 found on NP vs CM*)
- 1.5 x detection of cystic & solid masses with NP vs CM phase**
- Assessment of deenhancement for characterization
- Greatest temporal variability, however, depending on
 - Injection rate, contrast volume & cardiac output

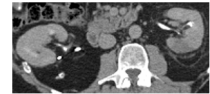
*Szolar et al., Radiology 1997;202:211

**Cohan et al. Radiology 1995;196:445



Radiology

Excretory Phase



- Identification and staging of upper tract transitional cell carcinoma
- Defines relationship of a central mass to the collecting structures
- Allows evaluation of de-enhancement* (Washout ROI at 15 minutes differentiates between hyperdense cyst and neoplasm)

*Macari, Bosniak. Radiology 1999;213:674



Radiology

Enhancement

- ROI should incorporate only the most attenuating portion of the lesion in all phases
- Avoid calcifications & low attenuation areas
- Minimal threshold value: 15 -20 HU
- Pseudoenhancement
 - Small cysts (<1.5 to 2 cm) "enhance" due to surrounding high attenuation (? Beam hardening, reconstruction algorithm)
 - Effect is greater with MDCT than single slice
 - Matrix detector array > adaptive array

Abdulla, et al. AJR 2002;179:1473



Radiology

Diagnosing Renal Lesions

- Cystic or Solid
- Lesion Margin
- Macroscopic & Microscopic Fat
- Density on non-contrast CT
- Echogenicity on US
- T2 Signal
- Enhancement pattern
 - CM, Nephrographic & Excretory phase
 - CT, MR and US



Radiology

Importance of Multiple Phases



Radiology

Alan J. Davidson, MD • Wendelin S. Hayes, DO • David S. Hartman, MD
William F. McCarthy, PhD • Charles J. Davis, Jr, Col, MC, USA

Renal Oncocytoma and Carcinoma: Failure of Differentiation with CT¹

The authors studied the ability to detect and characterize a renal mass arising in a kidney has been refined to an unprecedented degree over the past 2 decades due to technologic developments in sonography, computed tomography (CT), and magnetic resonance (MR) imaging (1-9). As these techniques have evolved, the varied imaging characteristics of renal masses have become apparent on the basis of both extensive formal investigations as well as a widely shared clinical experience. Criteria for the radiologic diagnosis of

Radiology. 1

State of the Art

Alan J. Davidson, MD • David S. Hartman, MD • Peter L. Choyke, MD • Brent J. Wagon, MD

Radiologic Assessment of Renal Masses: Implications for Patient Care¹

The ability to detect and characterize a renal mass arising in a kidney has been refined to an unprecedented degree over the past 2 decades due to technologic developments in sonography, computed tomography (CT), and magnetic resonance (MR) imaging (1-9). As these techniques have evolved, the varied imaging characteristics of renal masses have become apparent on the basis of both extensive formal investigations as well as a widely shared clinical experience. Criteria for the radiologic diagnosis of

agnostic of a certain pathologic condition, whereas others are equivocal (11,35,36,41-44). The use of multiple imaging modalities frequently produces data that are either redundant or contradictory. Further, radiologic interpretation is sometimes confounded by small size of the lesion (44,45). In any of these circumstances, the diagnostic radiologic effort may fail to provide data that usefully inform subsequent therapeutic choices and/or patient outcome.

Contemporary imaging has also uncovered a Pandora's box, revealing

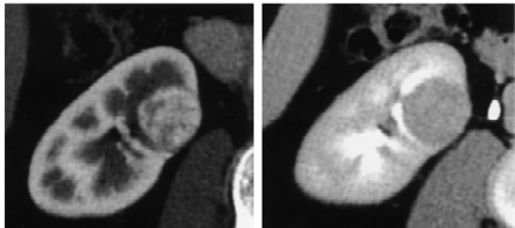
graphic features of the diagnoses under consideration.

PATHOLOGIC AND THERAPEUTIC BACKGROUND
There is an inherent linkage between the pathologic diagnosis of a mass, its radiologic analogue, and its therapeutic implication. For example, a radiologic diagnosis of a simple nephrogenic cyst made with near 100% confidence carries an implication of no subsequent therapy, con-



Radiology

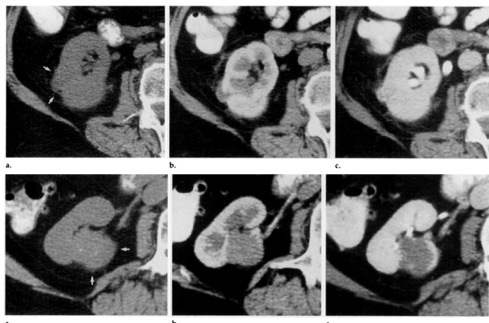
Importance of Multiple Phases



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Importance of Multiple Phases



Birnbaum Radiology 1996/200



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Early enhancement phase pitfalls

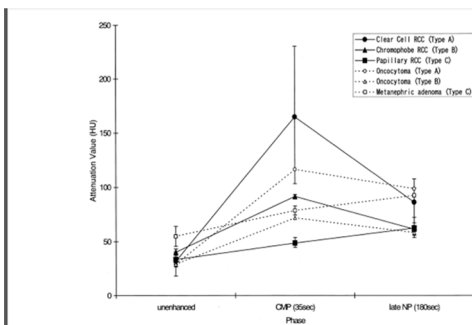
Hypovascular tumors may show slow enhancement not evident until and not evident until later phase



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Radiology

Enhancing Mass ≠ Cancer



Jinzaki, JCAT 2000



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Radiology

Solid Renal Cortical Tumors: Differentiation with CT¹

Figure 6

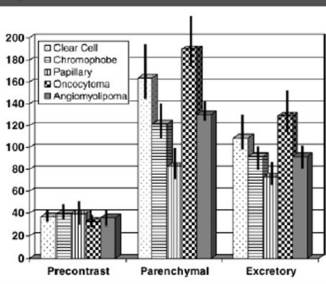


Figure 6: During the parenchymal phase, renal tumor subtypes demonstrate significantly different degrees of enhancement. Data in this graph were obtained by reader 2 and are the mean attenuation values (measured in Hounsfield units). Error bars are standard deviations.

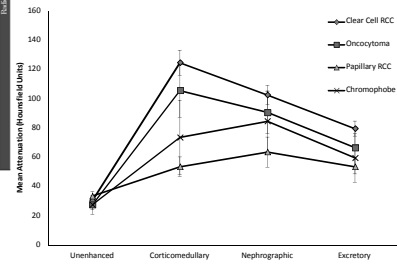


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RCC: Absolute CT Enhancement

Clear Cell Renal Cell Carcinoma: Discrimination from Other Renal Cell Carcinoma Subtypes and Oncocytoma at Multiphasic Multidetector CT¹



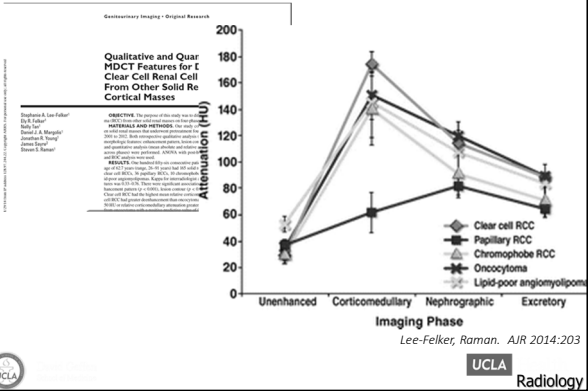
Young, Raman. Radiology 2013;267



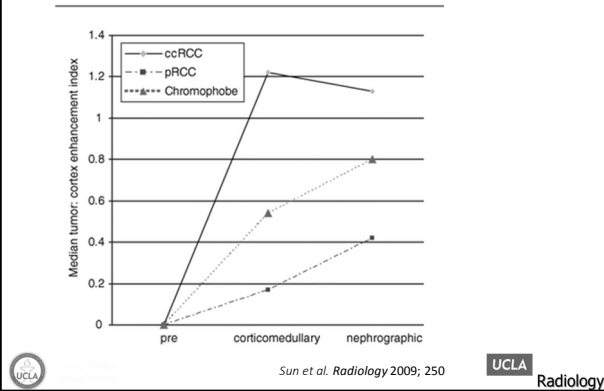
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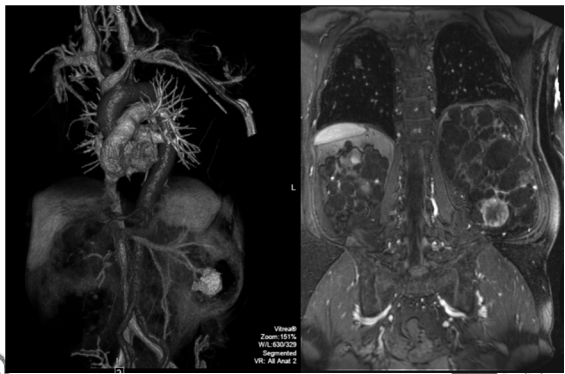
Absolute CT Enhancement



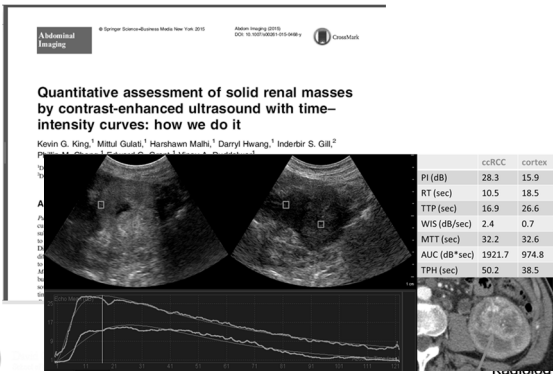
MRI Absolute Enhancement



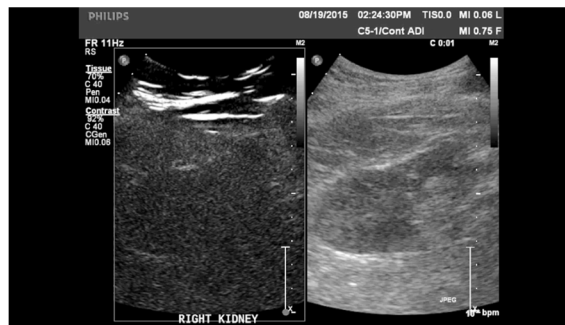
Dynamic Feraheme 3T MRI (4 mg/kg)



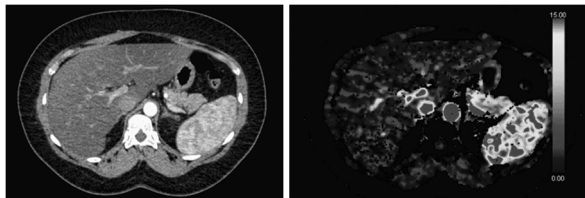
US Contrast: Clear Cell RCC



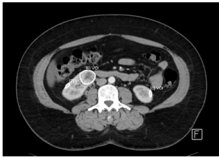
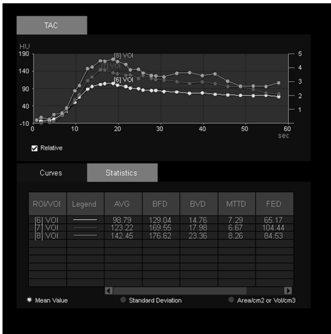
Contrast US: Clear Cell RCC



CT Perfusion: Clear Cell RCC

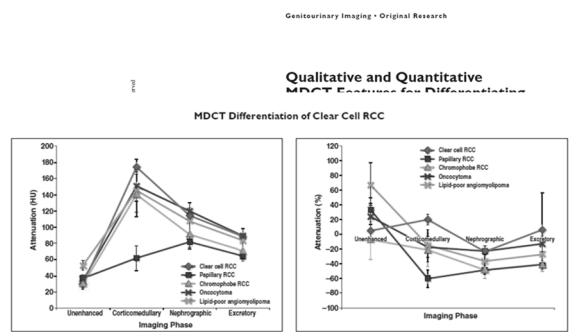


CT Perfusion: Clear Cell RCC



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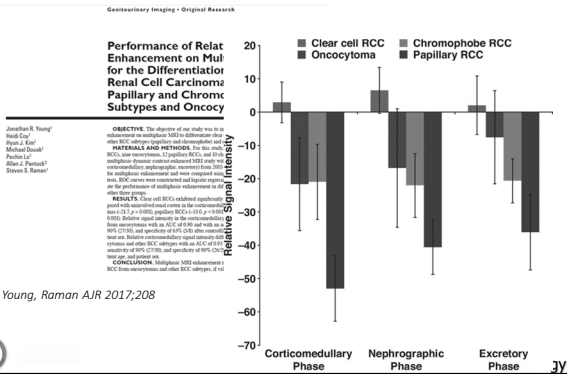
Relative Enhancement on MDCT



Lee-Felker, Raman. AJR 2014:203

UCLA Radiology

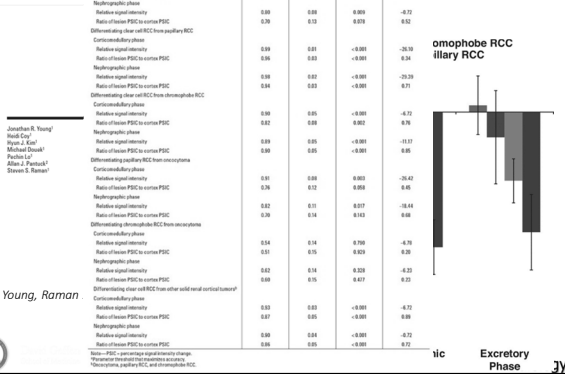
MR Imaging: Relative Enhancement



Young, Raman AJR 2017:208

UCLA Radiology

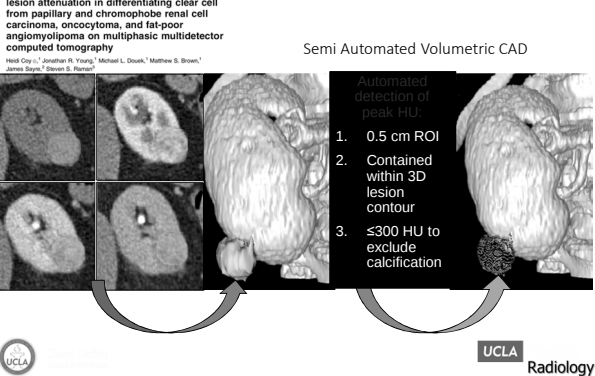
MR Imaging: Relative Enhancement



Young, Raman

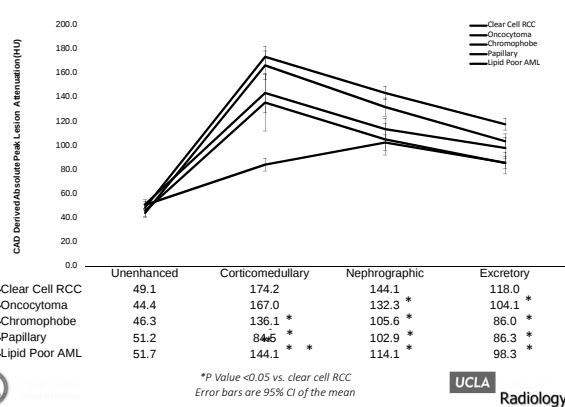
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CAD for RCC



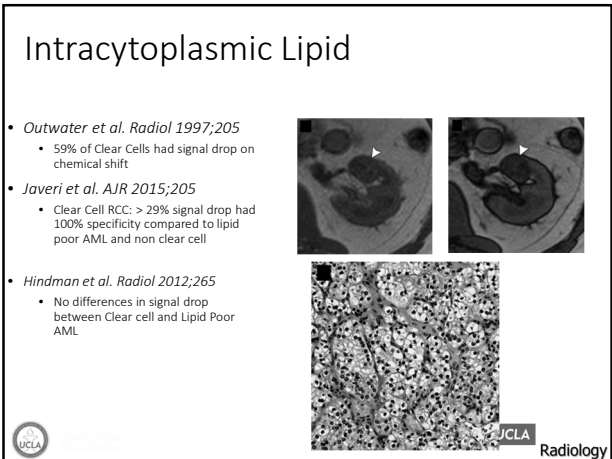
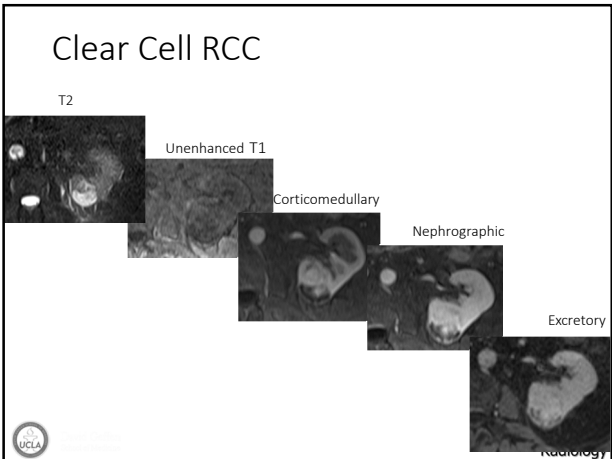
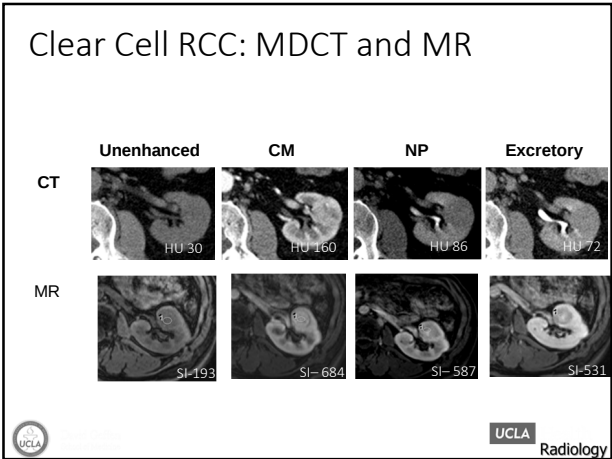
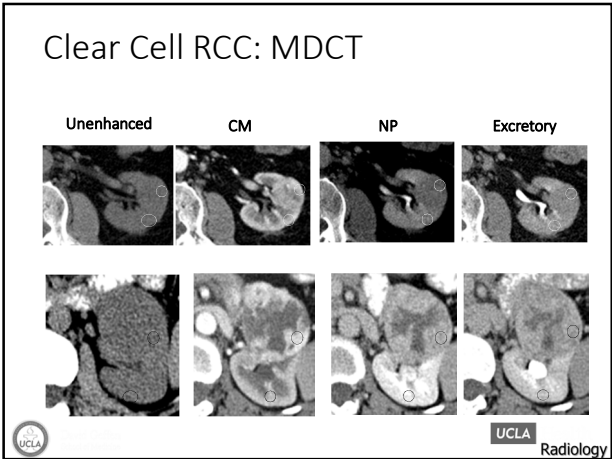
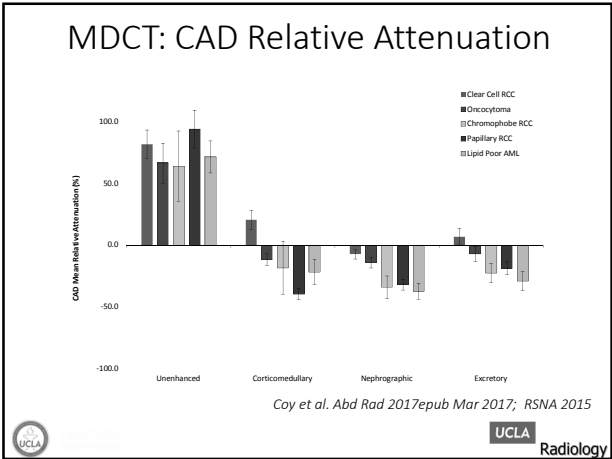
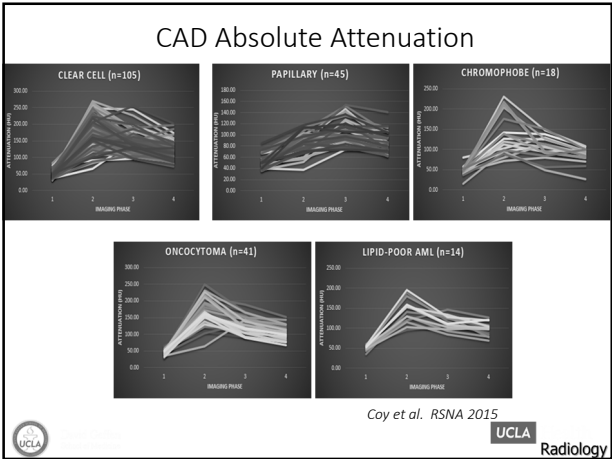
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CAD Absolute Attenuation

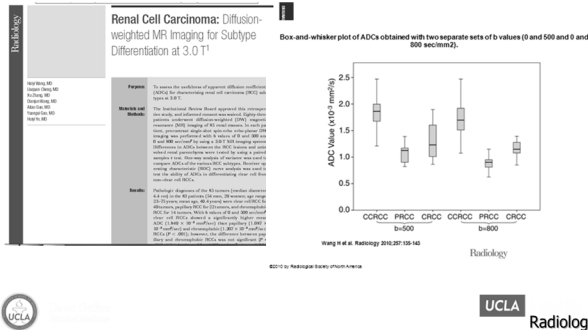


*P Value <0.05 vs. clear cell RCC
Error bars are 95% CI of the mean

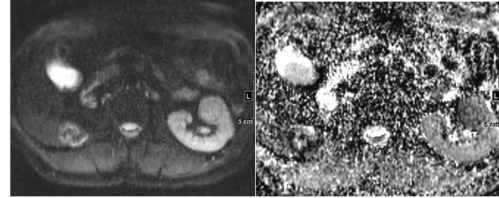
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Diffusion Weighted Imaging

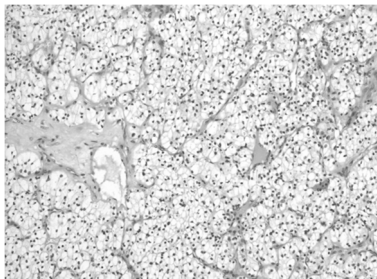


Clear Cell RCC: Diffusion



ADC $1.54 \times 10^{-3} \text{ mm}^2/\text{sec}$ at b value $1000 \text{ sec}/\text{mm}^2$

Clear Cell RCC

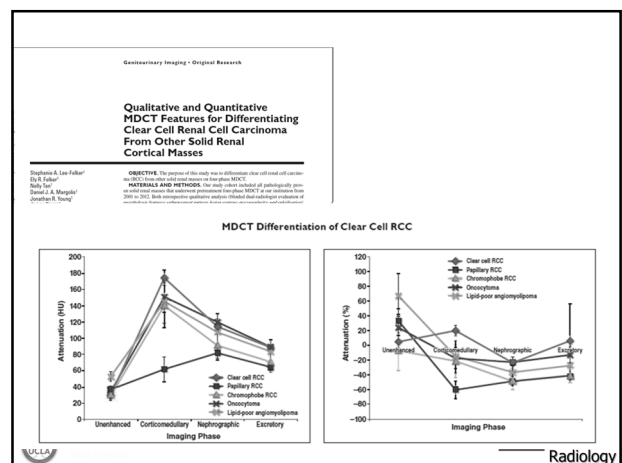


Clear Cell RCC

- Cystic or Solid: usually solid
- Presence of Macroscopic Fat: NO
- Density on non-contrast CT: Soft tissue
- Echogenicity on US: variable
- T2 Signal: High
- Enhancement pattern:
 - Absolute: peaks in CM phase
 - Relative: majority enhance above Cortex

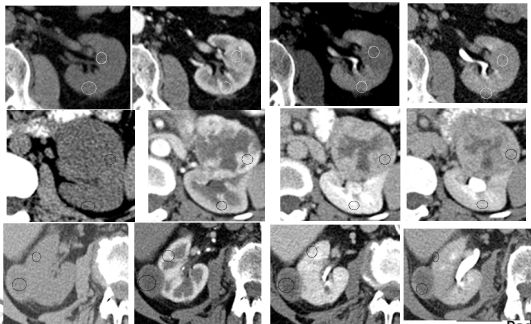
Papillary Renal Cell carcinoma

- 15% of renal cancers
- More likely to be multiple, bilateral
- Typically hypovascular, homogeneous
- Can be mistaken for cysts
- Enhance 10-30 HU
- Up to 60% T2 hypointense on MR



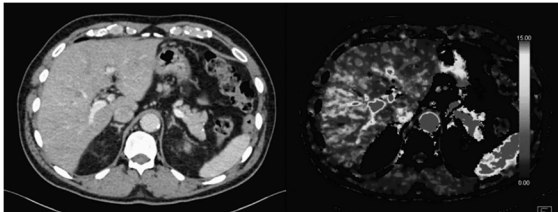
Papillary RCC: MDCT

Unenhanced CM NP Excretory



Radiology

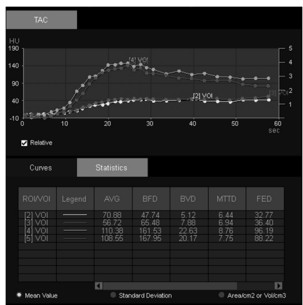
MDCT Perfusion: RCC



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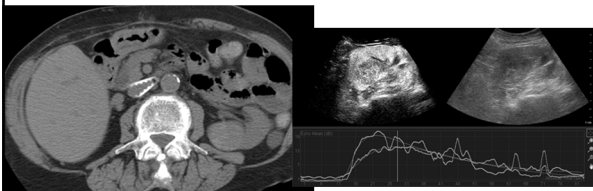
MDCT Perfusion: RCC



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US Papillary



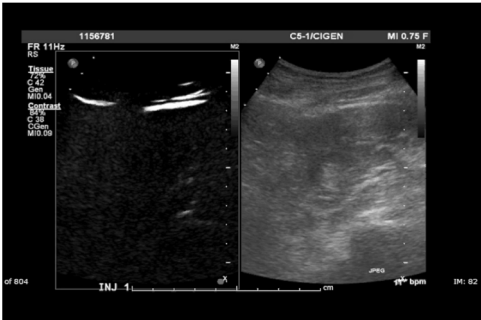
King et al. Abd Imaging 2015



UCLA

Radiology

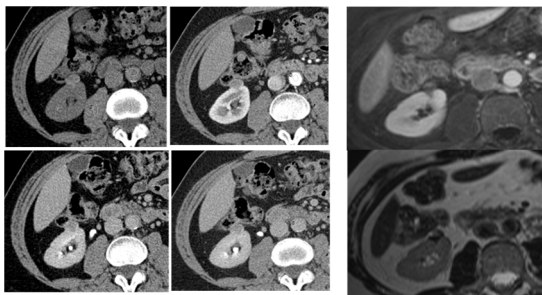
US Contrast: Papillary RCC



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Papillary RCC

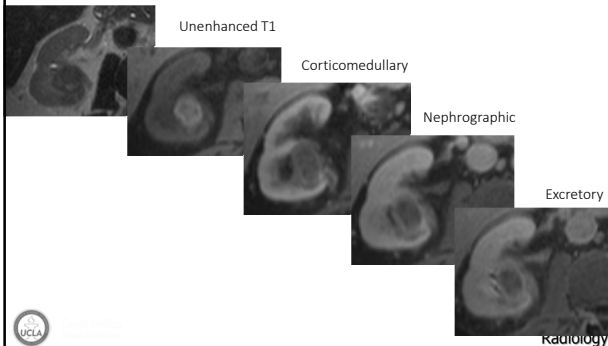


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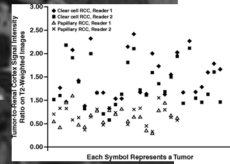
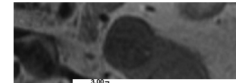
Papillary RCC

T2



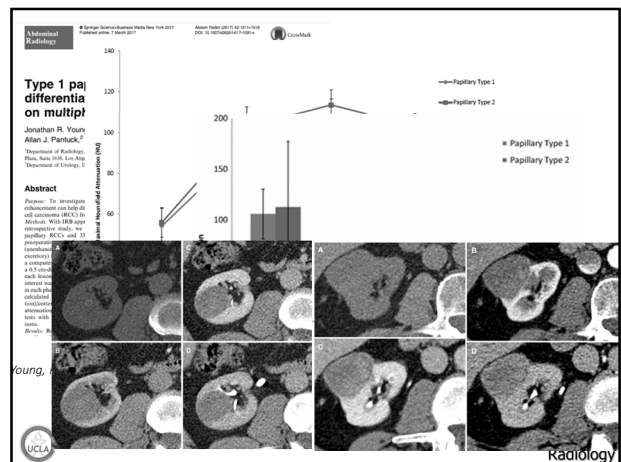
MRI Papillary RCC T2 Hypointensity

- *Oliva et al. AJR 2009;192*
 - 13-14/21 hypointense
 - None hyperintense
 - 17-21/28 Clear cell RCC hyperintense
- *Javeri et al. AJR 2015; 205*
 - 12/40 (30%) Clear Cell RCC hypointense
- *Hindman et al. Rad 2012; 265*
 - 10% Clear cell Hypo
 - 60% hyperintense

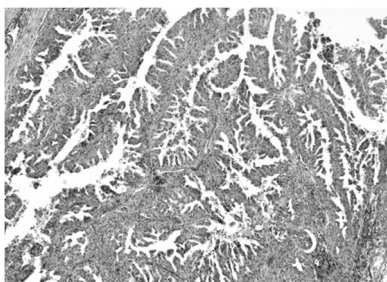


Subtypes of Papillary RCC

- Histopathologic subtype affects prognosis:
 - Type 1 papillary RCCs: 5-year survival rate of 95%
 - Type 2 papillary RCCs: 5-year survival rate of 66%



Papillary RCC

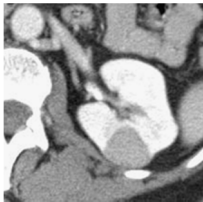


Papillary RCC

- Cystic or Solid: usually solid
- Presence of Macroscopic Fat: NO
- Density on non-contrast CT: normal to high (40-50 HU)
- Echogenicity on US: variable
- T2 Signal: low
- Enhancement pattern:
 - Absolute: low peak in Neph ph
 - Relative: below cortex
 - Excretory: Type II remains high (and larger)

Chromophobe RCC

- 5% of RCC
- Cytoplasm contains blue staining microvesicles on iron stain
- Good prognosis: 5 yr survival rate 90%
- CT features:
 - Large size
 - Homogeneously weak enhancement
 - Calcifications
 - No perinephric invasion



2.5 cm
44 → 115 HU



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Genitourinary Imaging • Original Research

Qualitative and Quantitative MDCT Features for Differentiating Clear Cell Renal Cell Carcinoma From Other Solid Renal Cortical Masses

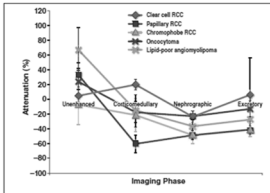
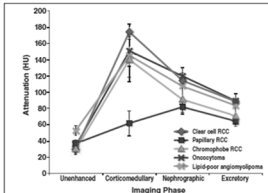
Hopkins & Lee-Feller
Ely R, Fisher
Rafiqi T
Daniel J, A. Bergs
Jonathan S. Young

OBJECTIVE: The purpose of this study was to differentiate clear cell renal cell carcinoma (ccRCC) from other renal cortical masses on baseline MDCT.

PURPOSE AND METHODS: Sixty renal masses, including 30 pathologically proven ccRCCs and 30 non-ccRCCs (15 papillary renal cell carcinomas [pRCCs], 15 chromophobe renal cell carcinomas [ChRCCs]), were retrospectively analyzed. MDCT features were compared between the two groups.

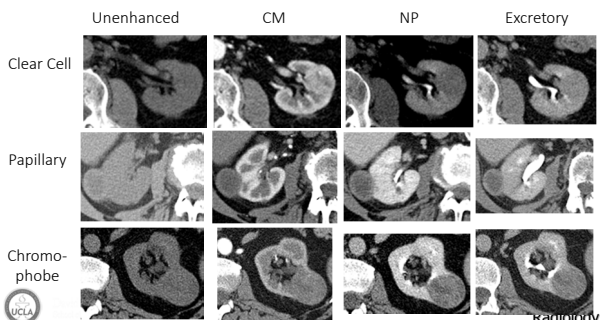
RESULTS: The mean size of the masses was 4.2 cm (range, 1.5–10.5 cm). The mean attenuation of the masses was 44 HU (range, 15–115 HU). The mean attenuation of the masses was 44 HU (range, 15–115 HU).

MDCT Differentiation of Clear Cell RCC



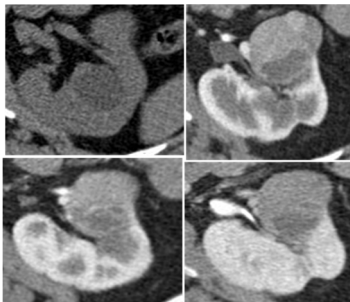
Radiology

Chromophobe RCC

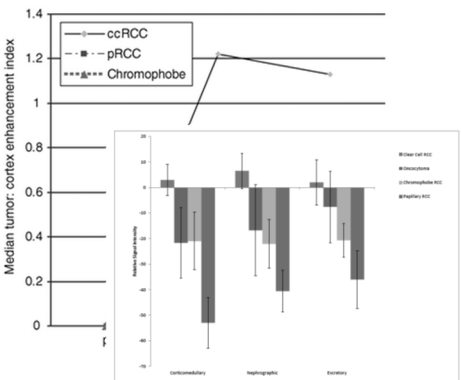


Radiology

Chromophobe RCC



Radiology



Radiology

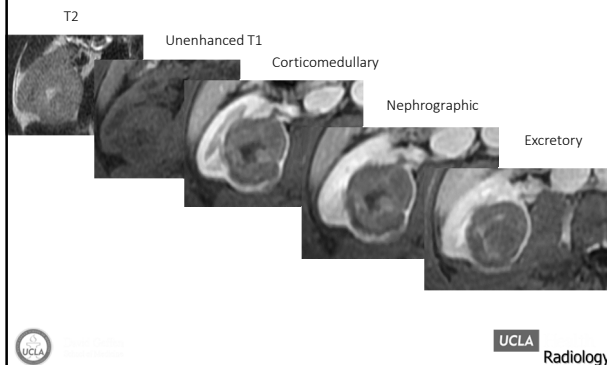
MR Ir

Imaging Measure	AUC	Standard Error	p	Percent Threshold
Differentiating clear cell RCC from non-clear cell RCC				
Contrast-enhanced T1-weighted	0.90	0.05	0.001	-17.7
Relative signal intensity	0.92	0.01	0.007	0.03
Ratio of lesion T1 to normal T1	0.99	0.00	0.000	-17.7
Relative signal intensity	0.99	0.00	0.000	0.02
Differentiating clear cell RCC from papillary RCC				
Contrast-enhanced T1-weighted	0.99	0.01	<0.001	-17.7
Relative signal intensity	0.99	0.00	<0.001	0.03
Ratio of lesion T1 to normal T1	0.99	0.00	<0.001	-17.7
Relative signal intensity	0.99	0.00	<0.001	0.02
Differentiating clear cell RCC from chromophobe RCC				
Contrast-enhanced T1-weighted	0.99	0.00	<0.001	-17.7
Relative signal intensity	0.92	0.00	0.002	0.76
Ratio of lesion T1 to normal T1	0.99	0.00	<0.001	-17.7
Relative signal intensity	0.99	0.00	<0.001	0.00
Differentiating papillary RCC from chromophobe RCC				
Contrast-enhanced T1-weighted	0.91	0.00	0.003	-17.7
Relative signal intensity	0.76	0.12	0.000	0.00
Ratio of lesion T1 to normal T1	0.92	0.01	0.017	-17.7
Relative signal intensity	0.76	0.14	0.003	0.00
Differentiating chromophobe RCC from non-clear cell RCC				
Contrast-enhanced T1-weighted	0.94	0.04	0.700	-17.7
Relative signal intensity	0.91	0.05	0.000	0.00
Ratio of lesion T1 to normal T1	0.92	0.04	0.000	-17.7
Relative signal intensity	0.90	0.05	0.017	0.02
Differentiating clear cell RCC from other solid renal cortical masses				
Contrast-enhanced T1-weighted	0.93	0.03	<0.001	-17.7
Relative signal intensity	0.97	0.00	<0.001	0.00
Ratio of lesion T1 to normal T1	0.90	0.04	<0.001	-17.7
Relative signal intensity	0.90	0.05	<0.001	0.02

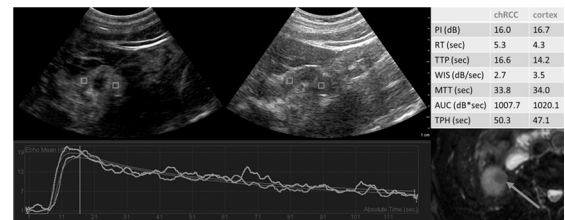


Radiology

Chromophobe RCC: MRI



US Contrast: Chromophobe

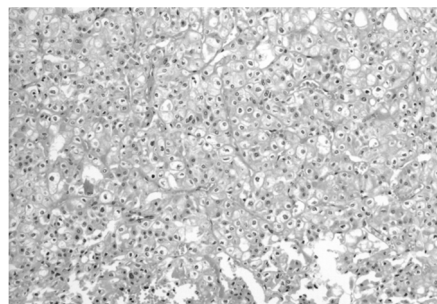


King et al. Abd Imaging 2015

Chromophobe

- Cystic or Solid: usually solid
- Presence of Macroscopic Fat: NO
- Density on non-contrast CT: normal to high
- Echogenicity on US: variable
- T2 Signal: iso to high
- Enhancement pattern :
 - Absolute: weak variable peak
 - Relative: below cortex

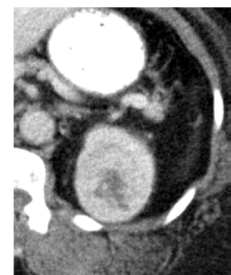
Chromophobe



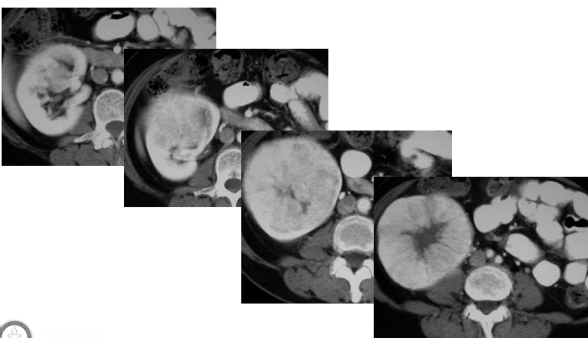
Benign Cortical Lesions

Oncocytoma

- Benign tumors (2-15%)
- Eosinophilic cytoplasm
- Solitary
- Male predominance
- Calcification rare
- Hypervascular
- Homogeneous
- Central scar



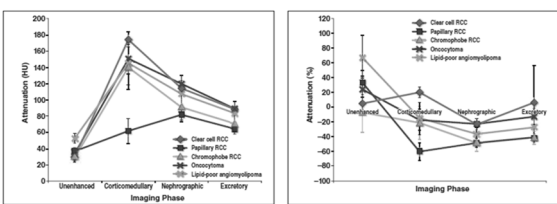
Oncocytoma



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MDCT Differentiation of Clear Cell RCC



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MR Imaging: Relative Enhancement

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Performance of Relative Enhancement on MRI for the Differentiation of Renal Cell Carcinoma Subtypes and Oncocytoma

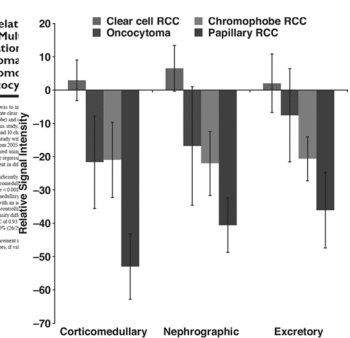
Jonathan S. Young¹, Heidi Coy², Ryan J. East³, Michael Douk⁴, Pasha Li⁵, Anne J. Petrella⁶, Steven S. Raman⁷

OBJECTIVE: The objective of our study was to evaluate the performance of multiphase MRI to differentiate clear cell renal cell carcinoma (cRCC), papillary renal cell carcinoma (pRCC), chromophobe renal cell carcinoma (chRCC), and oncocytoma (Onc) based on relative enhancement (RE) in the corticomedullary, nephrographic, and excretory phases.

RESULTS: One with RCC-related significantly greater RE was observed in the corticomedullary phase (p < 0.001) and in the nephrographic phase (p < 0.001). In the excretory phase, RE was significantly greater in the corticomedullary phase (p < 0.001) and in the nephrographic phase (p < 0.001). In the excretory phase, RE was significantly greater in the corticomedullary phase (p < 0.001) and in the nephrographic phase (p < 0.001).

CONCLUSION: Multiphase MRI enhancement in RCC subtypes was significantly different in the corticomedullary, nephrographic, and excretory phases.

Young, Raman AJR 2017;208



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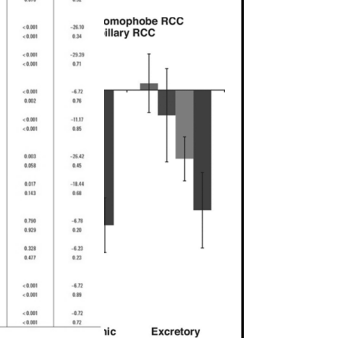
Radiology

MR Imaging: Relative Enhancement

TABLE 3: ROC Analysis to Evaluate the Performance of Corticomedullary and Nephrographic Enhancement Measures in Differentiating Clear Cell Renal Cell Carcinoma (RCC) From Oncocytoma and Other RCC Subtypes

Enhancement Measure	AUC	Standard Error	p	Positive Predictive Value
Differentiating clear cell RCC from oncocytoma				
Corticomedullary phase	0.98	0.05	<0.001	0.77
Nephrographic phase	0.92	0.11	<0.001	0.63
Excretory phase	0.98	0.08	<0.001	0.72
Differentiating clear cell RCC from papillary RCC				
Corticomedullary phase	0.98	0.05	<0.001	0.77
Nephrographic phase	0.96	0.03	<0.001	0.74
Excretory phase	0.98	0.02	<0.001	0.71
Differentiating clear cell RCC from chromophobe RCC				
Corticomedullary phase	0.98	0.05	<0.001	0.77
Nephrographic phase	0.92	0.08	<0.001	0.76
Excretory phase	0.98	0.05	<0.001	0.71
Differentiating clear cell RCC from papillary RCC and chromophobe RCC				
Corticomedullary phase	0.98	0.05	<0.001	0.77
Nephrographic phase	0.96	0.03	<0.001	0.74
Excretory phase	0.98	0.02	<0.001	0.71
Differentiating clear cell RCC from papillary RCC and chromophobe RCC and oncocytoma				
Corticomedullary phase	0.98	0.05	<0.001	0.77
Nephrographic phase	0.92	0.08	<0.001	0.76
Excretory phase	0.98	0.05	<0.001	0.71
Differentiating clear cell RCC from papillary RCC and chromophobe RCC and oncocytoma and papillary RCC				
Corticomedullary phase	0.98	0.05	<0.001	0.77
Nephrographic phase	0.92	0.08	<0.001	0.76
Excretory phase	0.98	0.05	<0.001	0.71
Differentiating clear cell RCC from papillary RCC and chromophobe RCC and oncocytoma and papillary RCC and chromophobe RCC				
Corticomedullary phase	0.98	0.05	<0.001	0.77
Nephrographic phase	0.92	0.08	<0.001	0.76
Excretory phase	0.98	0.05	<0.001	0.71

Young, Raman



UCLA

Radiology

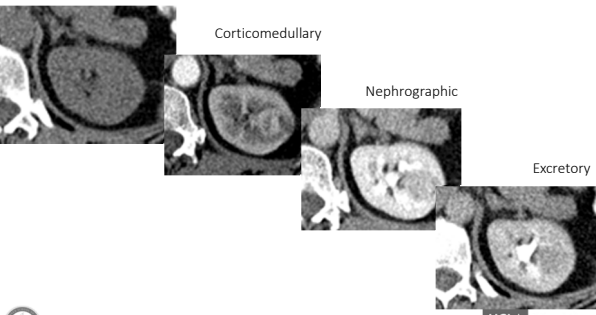
Oncocytoma

Unenhanced

Corticomedullary

Nephrographic

Excretory



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Oncocytoma

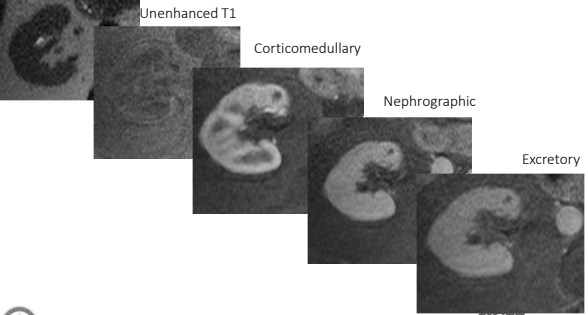
T2

Unenhanced T1

Corticomedullary

Nephrographic

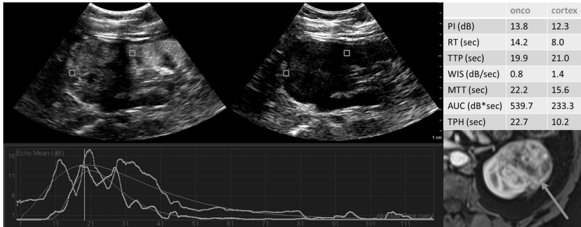
Excretory



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US Contrast: Oncocytoma



King et al. Abd Imaging 2015



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Oncocytoma vs Chromophobe

TABLE 2: Frequency of Assessed Qualitative Imaging Features in Renal Oncocytoma and Chromophobe Renal Cell Carcinoma

Feature	Reader 1			Reader 2		
	Renal Oncocytoma	Chromophobe Renal Cell Carcinoma	p	Renal Oncocytoma	Chromophobe Renal Cell Carcinoma	p
Peripheral location	92.9 (26/28)	86.7 (13/15)	0.5133	96.4 (27/28)	86.7 (13/15)	0.2635
Macroscopic fat	0.0 (0/28)	6.7 (1/15)	0.3967	0.0 (0/28)	0.0 (0/15)	1.0
Subcapsular hemorrhage	3.6 (1/28)	20.0 (3/15)	0.1143	0.0 (0/28)	6.7 (1/15)	0.3567
Hemorrhoids	7.1 (2/28)	6.7 (1/15)	0.9536	14.3 (4/28)	26.7 (4/15)	0.3306
T2 hyperintensity	46.4 (13/28)	40.0 (6/15)	0.6079	50.0 (14/28)	40.0 (6/15)	0.4461
T2 homogeneity	25.0 (7/28)	33.3 (5/15)	0.5679	14.3 (4/28)	33.3 (5/15)	0.1568
Cysts	14.3 (4/28)	0.0 (0/15)	0.2804	10.7 (3/28)	20.0 (3/15)	0.4118
Enhancement homogeneity	16.7 (5/28)	33.3 (5/15)	0.5842	0.0 (0/28)	26.7 (4/15)	0.0811
Concomitant phase hyperintensity	0.0 (0/28)	6.7 (1/15)	0.3967	3.6 (1/28)	13.3 (2/15)	0.2635
Nephrographic phase hyperintensity	0.0 (0/28)	0.0 (0/15)	1.0	3.6 (1/28)	6.7 (1/15)	0.6517
Excretory phase hyperintensity	0.0 (0/15)	0.0 (0/15)	1.0	7.1 (2/28)	0.0 (0/15)	0.5354
Central scar	50.0 (14/28)	33.3 (5/15)	0.2920	40.7 (11/28)	40.0 (6/15)	0.2502
Segmental enhancement invasion	26.6 (8/28)	13.3 (2/15)	0.3440	42.9 (12/28)	26.7 (4/15)	0.2960
Infiltrative margins	0.0 (0/28)	0.0 (0/15)	1.0	0.0 (0/28)	0.0 (0/15)	1.0
Perinephric fat invasion	16.7 (5/28)	6.7 (1/15)	0.6671	14.3 (4/28)	6.7 (1/15)	0.4697
Renal vein invasion	0.0 (0/28)	0.0 (0/15)	1.0	0.0 (0/28)	0.0 (0/15)	1.0

Note: Values are percentage with raw numbers in parentheses. No imaging feature had a statistically significant difference between renal oncocytoma and chromophobe renal cell carcinoma at $p < 0.05$.



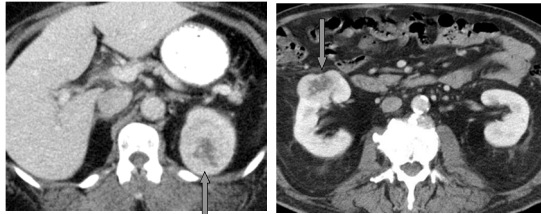
Rosenkranz et al. AJR 2010;195

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Oncocytoma: Central Scar

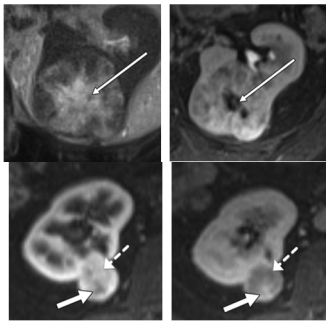
Oncocytoma

Renal Cell Carcinoma



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Oncocytoma: Scar & Segmental Inversion

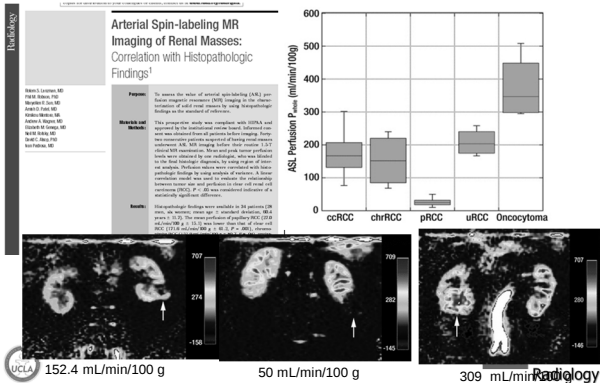


Rosenkranz et al. AJR 2010;195



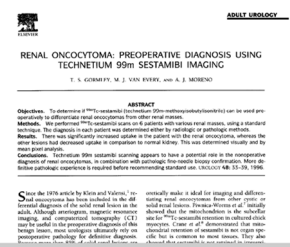
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MR: Arterial Spin-labeling



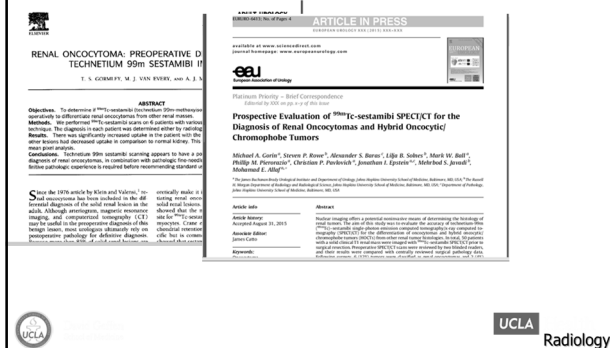
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Tc-99m Sestamibi

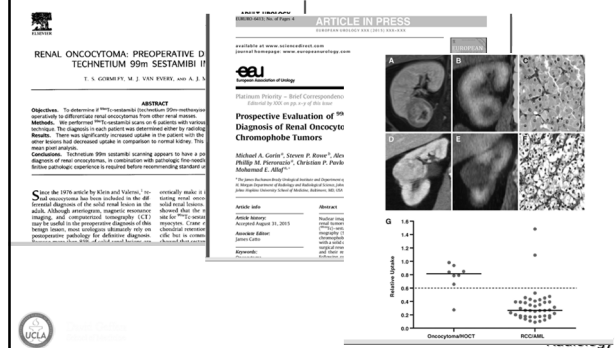


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Tc-99m Sestamibi



Tc-99m Sestamibi



Oncocytoma

- Cystic or Solid: usually solid
- Presence of Macroscopic Fat: NO
- Density on non-contrast CT: normal Echogenicity on US: variable
- T2 Signal: iso to high
- Enhancement pattern on CM, Neph and Excretory phase: peaks in CM but < 100HU and less than cortex with weak washout

Fat Poor Angiomyolipoma

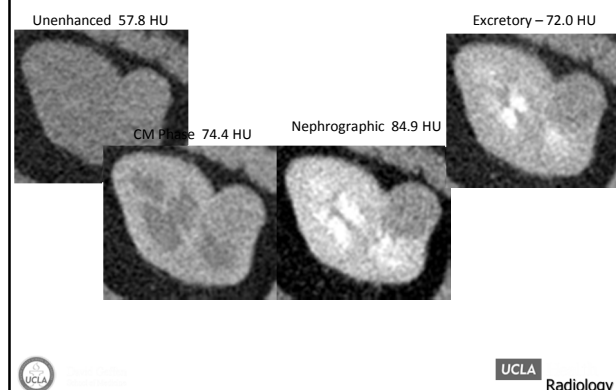
- 10% of AML
- Echogenic on US
- Uniformly hyperdense on CT
- Low T2 signal on MR
- May occasionally drop out on opposed phase
- Peak enhances in the arterial phase

Fat Poor Angiomyolipoma

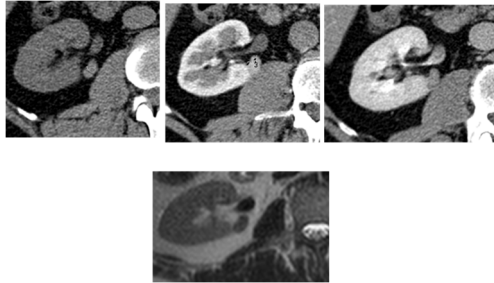
- CT/US/MR findings in 6 cases of AML composed of smooth muscle and minimal fat were compared with 100 RCC:
- Homogeneously high attenuation of mass on CT without contrast
- Homogeneous enhancement post contrast
- Homogeneous isoechogenicity on sonography
- Protrusion of lesion beyond renal margin without a beak
- Low signal intensity on T2 weighted MR images

Jinzaki et al. Radiology 1997;205

Fat Poor Angiomyolipoma

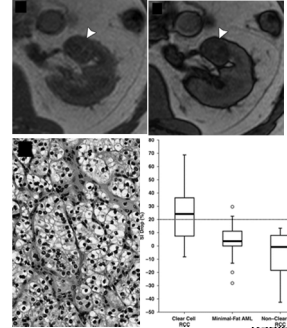


Fat Poor Angiomyolipoma

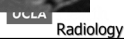
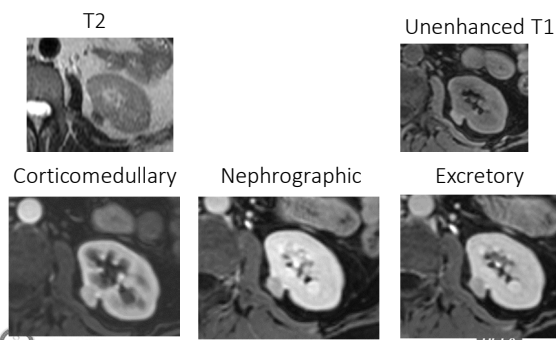


Intracytoplasmic Lipid

- *Outwater et al. Radiol 1997;205*
 - 59% of Clear Cells had signal drop on chemical shift
- *Javeri et al. AJR 2015;205*
 - Clear Cell RCC: > 29% signal drop had 100% specificity compared to lipid poor AML and non clear cell
- *Hindman et al. Radiol 2012;265*
 - No differences in signal drop between Clear cell and Lipid Poor AML.

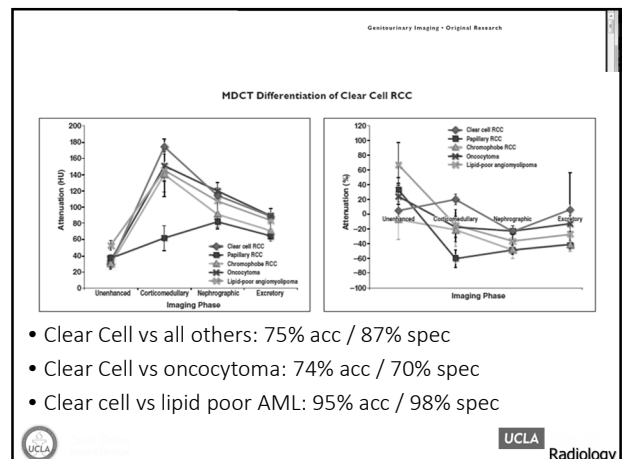
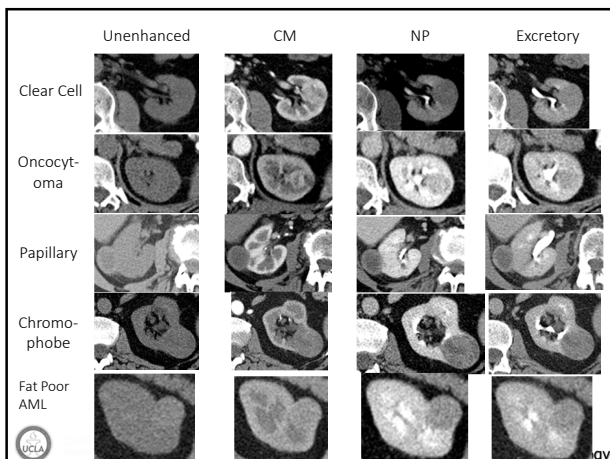


Fat-Poor Angiomyolipoma



Fat Poor Angiomyolipoma

- Cystic or Solid: usually solid
- Presence of Macroscopic Fat: NO
- Density on non-contrast CT: high to very high
- Echogenicity on US: variably high
- T2 Signal: mainly low
- Enhancement pattern on CM, Neph and Excretory phase: low but peaks in CM



Imaging Based Prediction of RCC Biology



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Can CT be used to predict RCC Grade ?

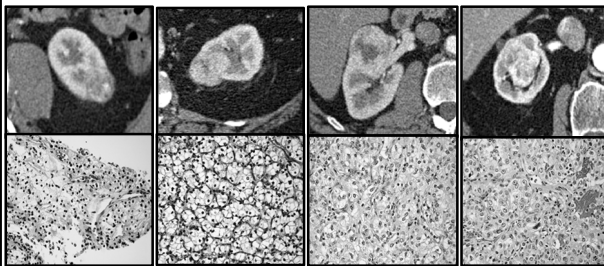


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Fuhrman Grade

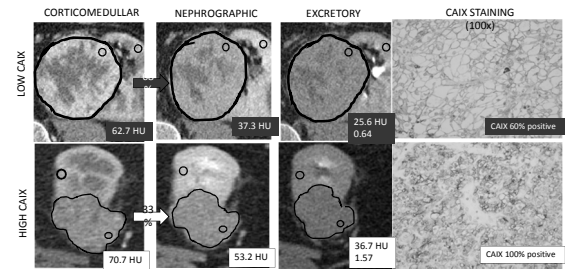
Stratifies tumor grade on the basis of nuclear size and shape, and the prominence of nucleoli

Grade I Grade II Grade III Grade IV



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MDCT Features May Correlate with CA IX Stains:



Coy et al. RSNA 2017



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Can MDCT Imaging Features Discriminate Common Subtypes of RCC from Aggressive RCC Variants?



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Aggressive RCC Variants

- Sarcomatoid RCC and collecting duct carcinoma should be managed differently than more common RCC subtypes, namely clear cell.
 - Clear cell RCCs are typically surgically resected
 - For sarcomatoid RCC and collecting duct carcinoma, surgical resection prior to systemic therapy may actually worsen outcomes
 - 45-84% of patients with collecting duct and sarcomatoid RCC have distant metastases at the time of diagnosis.



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Aggressive Variants

Original Investigation

Sarcomatoid Renal Cell Carcinoma and Collecting Duct Carcinoma: Discrimination From Common Renal Cell Carcinoma Subtypes and Benign RCC Mimics on Multiphasic MDCT

Jennifer A. Young, MD, Jessica R. Young, MD, David J. A. Margolis, MD, Steven S. Raman, MD

Background: Sarcomatoid renal cell carcinoma (SRCC) and collecting duct carcinoma (CDC) are aggressive variants of renal cell carcinoma (RCC) that are histologically distinct from common RCC subtypes. These variants are often associated with a poor prognosis and may be difficult to distinguish from benign RCC mimics on multiphasic MDCT. The purpose of this study was to evaluate the ability of multiphasic MDCT to discriminate SRCC and CDC from common RCC subtypes and benign RCC mimics.

Methods: A retrospective review of multiphasic MDCT scans of the kidneys was performed. All cases of SRCC and CDC were identified and compared to common RCC subtypes and benign RCC mimics. The imaging features were evaluated for their ability to discriminate between the two groups.

Results: A total of 10 cases of SRCC and 10 cases of CDC were identified. The imaging features of these variants were compared to those of common RCC subtypes and benign RCC mimics. The results showed that SRCC and CDC can be discriminated from common RCC subtypes and benign RCC mimics on multiphasic MDCT.

Conclusion: Multiphasic MDCT can be used to discriminate SRCC and CDC from common RCC subtypes and benign RCC mimics. This information can be used to guide management decisions.

	Infiltrative Spread Pattern	Irregular Contour
Sensitivity (%)	82 (8/11)	64 (7/11)
Specificity (%)	93 (28/30)	98 (30/30)
Positive Predictive Value (%)	30 (3/10)	58 (7/12)
Negative Predictive Value (%)	99 (28/29)	99 (30/30)

SRCC, sarcomatoid renal cell carcinoma.

Young Acad Rad 2017

UCLA Radiology

Can CT Texture Feature Analysis Discriminate RCC Subtypes from Benign Mimics?

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CT Texture Features

- Texture features are measurements that quantitatively characterize lesion heterogeneity by evaluating the distribution of voxel densities within a lesion.
- Have been used to evaluate pulmonary nodules and gastric malignancies
- Few studies have utilized texture features to evaluate renal masses.

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Texture Features

- Texture Features:
 - 89% of Oncocytomas
 - 91% of ccRCC
 - 100% Papillary

CT Texture Analysis of Renal Masses:

Gastrointestinal Imaging - Original Research

Small (< 4 cm) Renal Mass: Differentiation of Oncocytoma From Renal Cell Carcinoma on Biphasic Contrast-Enhanced CT

Small et al.
Radiology 2015; 205

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Clear Cell Renal Cell Carcinoma: Multiphasic Multidetector CT Imaging Features Help Predict Genetic Karyotypes¹

Steven C. Sack, MD, Margaret L. Liu, MD, David J. A. Margolis, MD, David J. A. Margolis, MD, Rachel P. Sack, MD, Ron L. Lohman, MD, Alan J. Parke, MD, Steven S. Raman, MD

Purpose: To determine whether imaging characteristics at multiphasic multidetector computed tomography (CT) correlate with common karyotypic abnormalities in patients with clear cell renal cell carcinoma (ccRCC).

Materials and Methods: Institutional review board approval was obtained, and informed consent was waived for this HIPAA-compliant retrospective study. From January 2008 through September 2009, the preoperative multiphasic (corticomedullary, nephrographic, and excretory phases) multidetector helical CT scans of 100 patients with pathologically confirmed ccRCC were reviewed.

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CT Texture Analysis of Renal Masses:

Gastrointestinal Imaging - Original Research

Small (< 4 cm) Renal Mass: Differentiation of Oncocytoma From Renal Cell Carcinoma on Biphasic Contrast-Enhanced CT

Small et al.
Radiology 2015; 205

Feature and Characteristic	Less of 2 (n = 20)	No Less of 2 (n = 10)	Less of 2 (n = 10)	No Less of 2 (n = 10)	Less of 2 (n = 10)	No Less of 2 (n = 10)
Group 1: Oncocytoma	10/20	10/10	0/0	10/10	0/0	10/10
Group 2: ccRCC	10/10	10/10	0/0	10/10	0/0	10/10
Group 3: Papillary	10/10	10/10	0/0	10/10	0/0	10/10
Group 4: Unclassified	10/10	10/10	0/0	10/10	0/0	10/10

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Radiogenomics of Clear Cell Renal Cell Carcinoma: Associations between CT Imaging Features and Mutations¹

Authors: Christoph A. Kralic, MD; Pier Luigi Di Paolo, MD; Joshua Chien, DO; A. Ali Hakeem, MD; Inna Ostromova, PhD; Paul Russo, MD, FACS; Hideo Hsieh, MD, PhD, DrPH; Robert Mizer, MD; James J. Hsieh, MD, PhD; Omer Niaz, MD.

Purpose: To investigate associations between computed tomographic (CT) features of clear cell renal cell carcinoma (RCC) and mutations in *VHL*, *PBRM1*, *SETD2*, *KDM5C*, or *BAPI* genes.

Materials and Methods: The institutional review board approved this retrospective, hypothesis-generating study of 223 patients with clear cell RCC and waived the informed consent requirement. The study was HIPAA compliant. Three radiologists independently reviewed pretreatment CT images of all clear cell RCCs without knowledge of their genomic profile. One radiologist measured largest diameter and enhancement parameters of each clear cell RCC. Associations between CT features and mutations in *VHL*, *PBRM1*, *SETD2*, *KDM5C*, and *BAPI* genes were tested by using the Fisher

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Radiogenomics of Clear Cell Renal Cell Carcinoma: Associations between CT Imaging Features and Mutations¹

Figure 2

Subject-based color map illustrates mutations and CT features.

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Table 2

CT Features and Mutations

CT Feature	<i>VHL</i>			<i>PBRM1</i>			<i>SETD2</i>			<i>BAPI</i>			<i>KDM5C</i>		
	Count	Present	P Value	Count	Present	P Value	Count	Present	P Value	Count	Present	P Value	Count	Present	P Value
Enhancement															
Nephrons															
Absent (n = 17)	55 (0.10)	41 (0.2)	.224	62 (0.10)	11 (0.2)	.103	62 (0.10)	17 (0.3)	.116	94 (0.10)	5 (0.1)	>.39	94 (0.10)	5 (0.1)	>.39
Present (n = 216)	45 (0.09)	542 (0.17)	.324	69 (0.10)	30 (0.05)	.183	65 (0.02)	6 (0.04)	.116	94 (0.02)	6 (0.01)	>.39	95 (0.01)	6 (0.01)	>.39
Corticomedullary															
Absent (n = 18)	45 (0.08)	51 (0.09)	.345	69 (0.10)	30 (0.05)	.183	65 (0.02)	7 (0.04)	.116	95 (0.02)	4 (0.01)	.39	95 (0.02)	4 (0.01)	.39
Present (n = 205)	42 (0.01)	59 (0.01)	.345	70 (0.02)	23 (0.01)	.305	94 (0.02)	5 (0.01)	.77	88 (0.02)	11 (0.01)	.09	92 (0.02)	10 (0.01)	.09
Reinforced margin															
Absent (n = 118)	38 (0.05)	61 (0.07)	.009	71 (0.04)	28 (0.04)	>.99	82 (0.02)	6 (0.01)	.805	96 (0.04)	3 (0.01)	.004	94 (0.02)	5 (0.01)	.31
Present (n = 105)	30 (0.06)	44 (0.01)	.009	71 (0.05)	20 (0.02)	>.99	82 (0.02)	7 (0.01)	.805	95 (0.01)	8 (0.01)	.004	95 (0.01)	8 (0.01)	.004
Renal vein invasion															
Absent (n = 198)	47 (0.02)	53 (0.02)	>.99	71 (0.04)	28 (0.02)	>.99	82 (0.04)	7 (0.04)	.726	95 (0.02)	4 (0.01)	.002	94 (0.02)	5 (0.01)	.019
Present (n = 25)	42 (0.01)	54 (0.01)	>.99	71 (0.02)	28 (0.01)	>.99	91 (0.02)	8 (0.01)	.726	87 (0.02)	14 (0.01)	.002	82 (0.02)	17 (0.01)	.019
Collecting system															
Involved															
Absent (n = 210)	47 (0.02)	53 (0.02)	.588	72 (0.04)	27 (0.02)	.528	83 (0.02)	6 (0.01)	.511	97 (0.02)	7 (0.01)	.015	92 (0.02)	7 (0.01)	.015
Present (n = 20)	40 (0.01)	58 (0.01)	.588	65 (0.01)	34 (0.01)	.528	87 (0.02)	12 (0.01)	.264	96 (0.02)	14 (0.01)	.017	96 (0.01)	13 (0.01)	.017
Not involved															
Absent (n = 216)	44 (0.02)	55 (0.01)	.017	69 (0.02)	30 (0.02)	.017	81 (0.02)	7 (0.01)	.373	95 (0.02)	6 (0.01)	.012	95 (0.02)	7 (0.01)	.015
Present (n = 10)	72 (0.04)	28 (0.01)	.017	94 (0.01)	5 (0.01)	.017	100 (0.01)	0	.373	100 (0.01)	0	.012	100 (0.01)	0	.015
Mutational tumor															
Unenhanced															
Absent (n = 48)	63 (0.02)	34 (0.01)	.018	81 (0.02)	18 (0.01)	.008	94 (0.02)	13 (0.01)	.101	92 (0.01)	6 (0.01)	.723	97 (0.02)	2 (0.01)	.018
Present (n = 188)	42 (0.01)	57 (0.01)	.018	68 (0.02)	31 (0.02)	.008	84 (0.02)	5 (0.01)	.101	94 (0.02)	5 (0.01)	.723	95 (0.02)	7 (0.01)	.018
Enhanced															
Absent (n = 78)	35 (0.02)	64 (0.01)	.026	74 (0.02)	25 (0.01)	.04	89 (0.02)	10 (0.01)	.285	97 (0.01)	2 (0.01)	.15	99 (0.02)	10 (0.01)	.173
Present (n = 145)	52 (0.01)	47 (0.01)	.026	69 (0.02)	31 (0.01)	.04	94 (0.02)	5 (0.01)	.285	92 (0.02)	7 (0.01)	.15	94 (0.02)	5 (0.01)	.173

Note: Data are percentages, and numbers in parentheses are used to calculate the percentages except where otherwise indicated. P values are from Fisher exact test, and Fisher's values are from likelihood-governed analysis.

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Abdominal Imaging

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Abdom Imaging (2014)
DOI: 10.1007/s00261-014-0092-2

Clear cell renal cell carcinoma: multiphasic MDCT enhancement can predict the loss of chromosome 8p

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²Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Abstract

Purpose: To investigate whether imaging features on multiphasic multidetector computed tomography (MDCT) can predict the loss of chromosome 8p in clear

Conclusion: Enhancement on multiphasic MDCT can predict the loss of 8p in clear cell RCCs and can thus provide a non-invasive means of guiding further management, including surgery, ablation, watchful waiting, or medical management.

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Abdom Imaging

Cle MD of

Jonati
Jocely
Plaza, S
Depart

Absti

Purpose
multiph
(MDCT)

Mean Attenuation (Hounsfield Units)

Phase

Loss of 8p

Without Loss of 8p

Unenhanced

Corticomedullary

Nephrographic

Excretory

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Unenhanced

CM

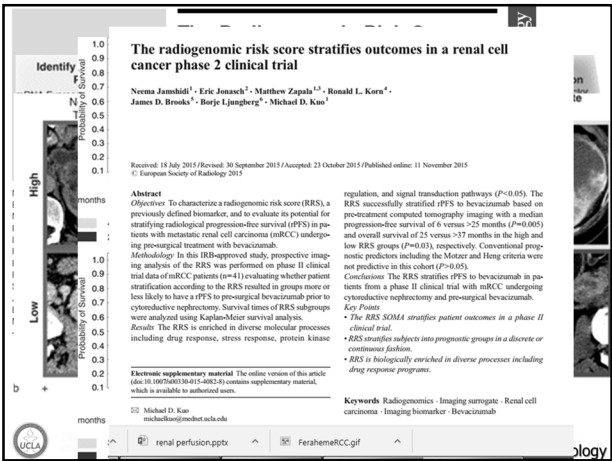
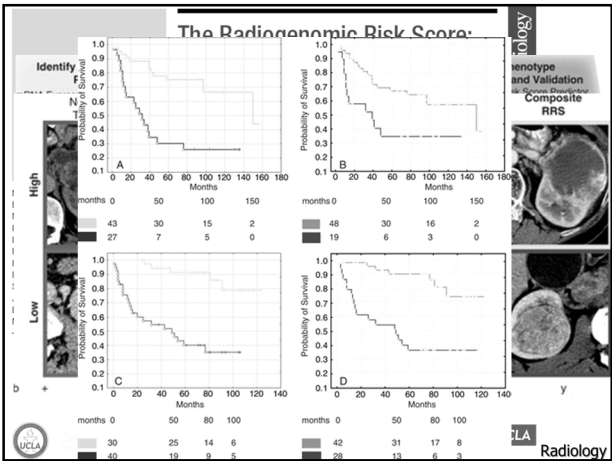
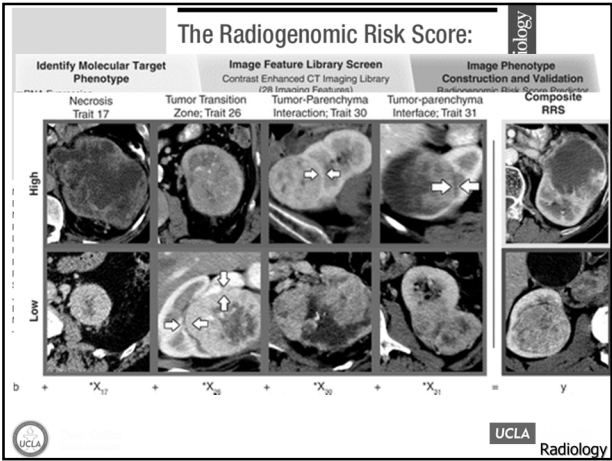
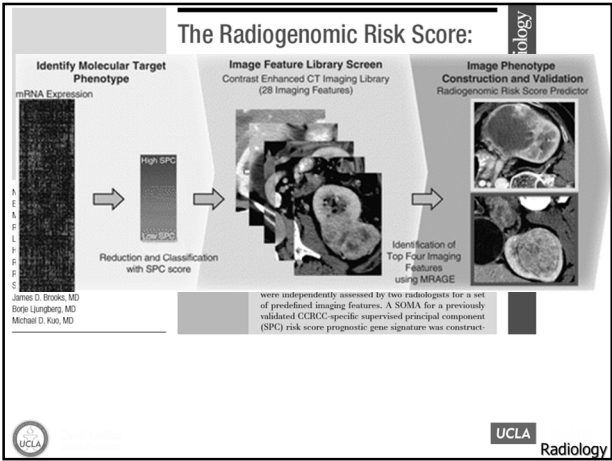
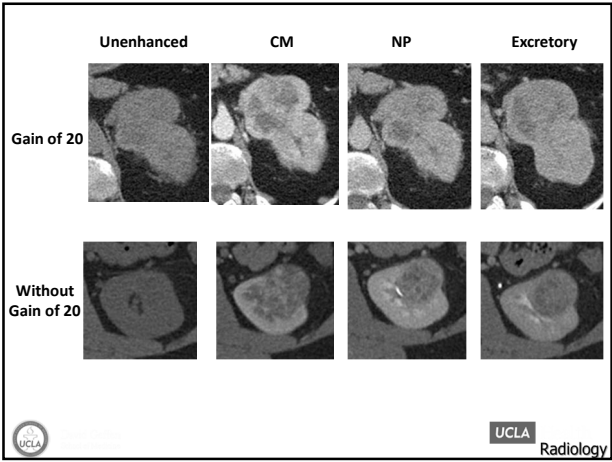
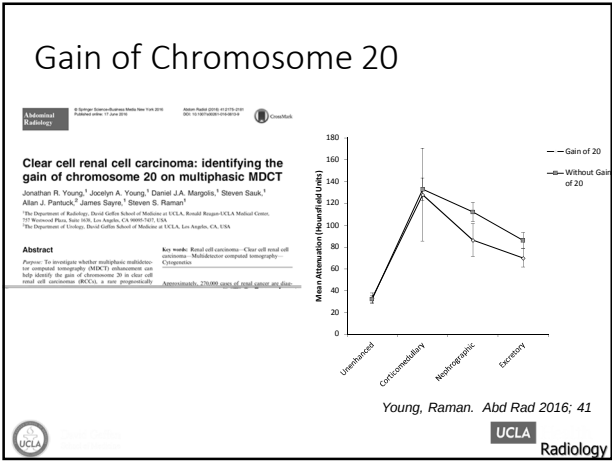
NP

Excretory

Loss of 8p

Without Loss of 8p

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Summary

- A significant minority of renal masses are benign
- Cystic renal lesions are indolent
- Solid renal masses grow 2-3 mm/yr
- Biopsy is very effective for discrimination
- Imaging can characterize the majority of renal masses
- Imaging can help grade clear cell RCC
- Imaging can possibly distinguish papillary type 1 from type 2
- Imaging can help predict clear cell cytogenetics
- Biopsy is safe and effective



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Summary

- Multiphasic CT & MR are necessary for characterization
- Imaging can characterize the majority of renal masses
- Imaging can help grade clear cell RCC
- Imaging can possibly distinguish papillary type 1 from type 2
- Imaging can help predict clear cell cytogenetics

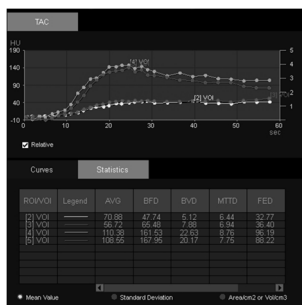


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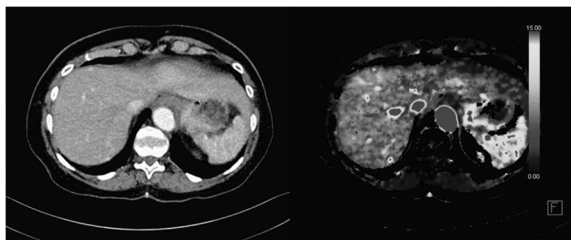
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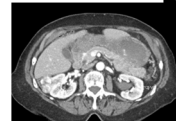
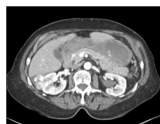
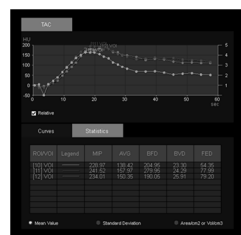
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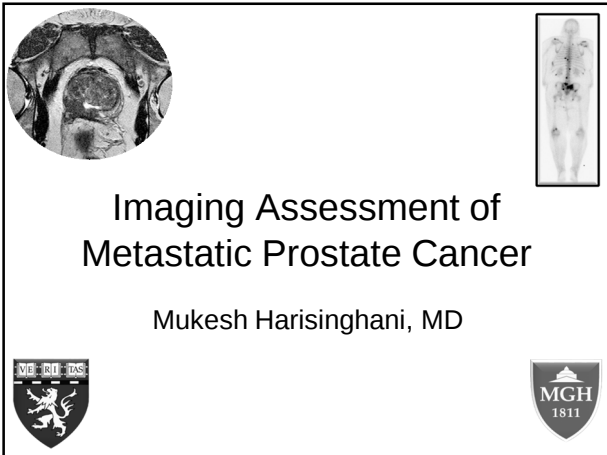
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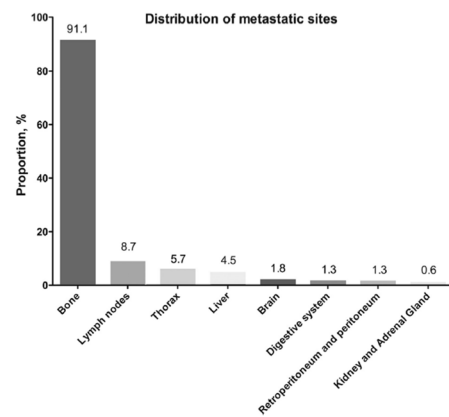


Disclosures

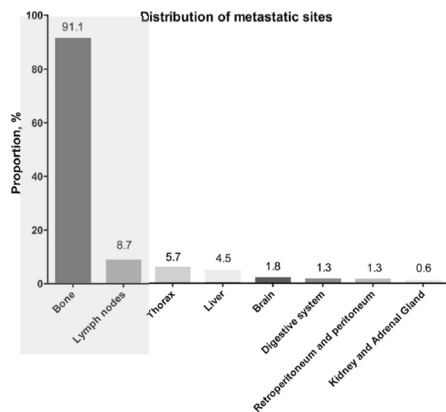
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Overview

- Clinical overview of metastatic prostate cancer
- Imaging techniques
 - Benefits and Limitations



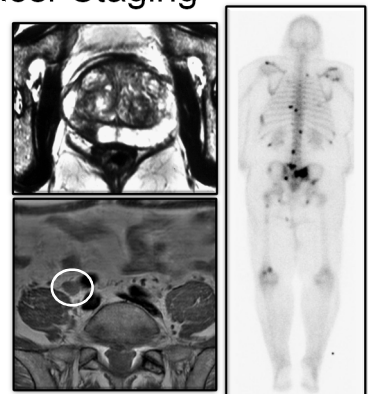
EUROPEAN UROLOGY 68(2015)325–334



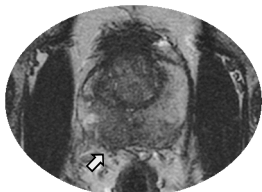
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Prostate Cancer Staging

- T Staging
- Nodal Staging
- Metastases

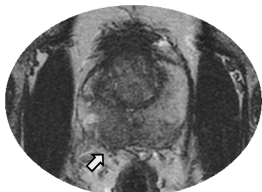


Prostate Cancer



T3 non organ confined tumor →
adjuvant radiotherapy after surgery or
adjuvant hormone therapy after
radiotherapy

Prostate Cancer

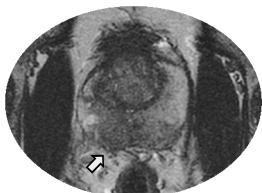


T3 non organ confined tumor →
adjuvant radiotherapy after surgery or
adjuvant hormone therapy after
radiotherapy

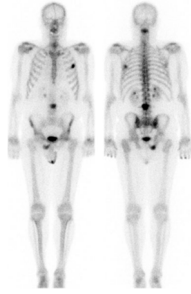


N1 spread to regional LN →
recommendation is androgen
deprivation therapy → increasingly
recognized as benefiting from
radiotherapy

Prostate Cancer



T3 non organ confined tumor →
adjuvant radiotherapy after surgery or
adjuvant hormone therapy after
radiotherapy



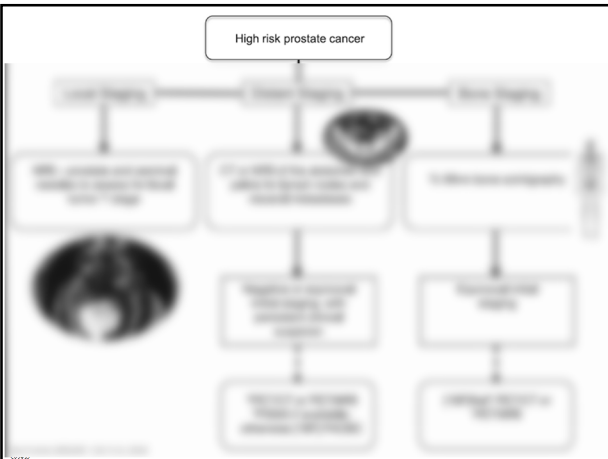
M1 distant metastases → asymptomatic
→ at this time unproven to benefit from
initial local therapy

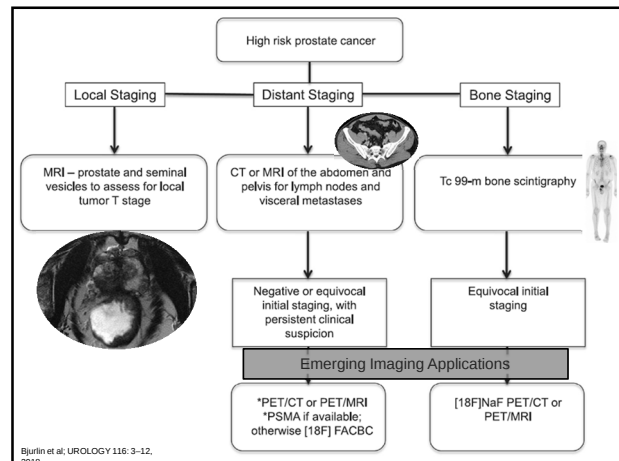
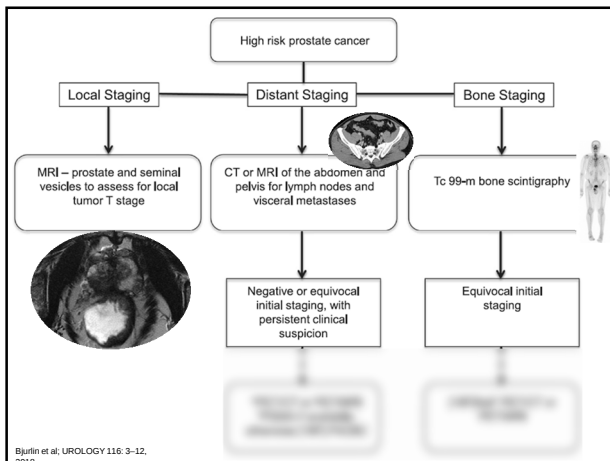
NCCN Risk Stratification for PCa

Risk Category	Clinical T Stage	Gleason Score	PSA (ng/mL)
Very low ^a	T1c	≤6 (Fewer than 3 cores each with ≤50% cancer)	<10 (PSA density <0.15 ng/mL/g)
Low ^b	T1-T2a	≤6	<10
Intermediate ^b	T2b-T2c	7	10-20
High ^b	T3a	8-10	>20
Very high ^b	T3b-T4	Primary pattern 5 or >4 cores with Gleason score 8-10	—

NCCN Risk Stratification for PCa

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High ^b	T3a	8-10	>20
Very high ^b	T3b-T4	Primary pattern 5 or >4 cores with Gleason score 8-10	—





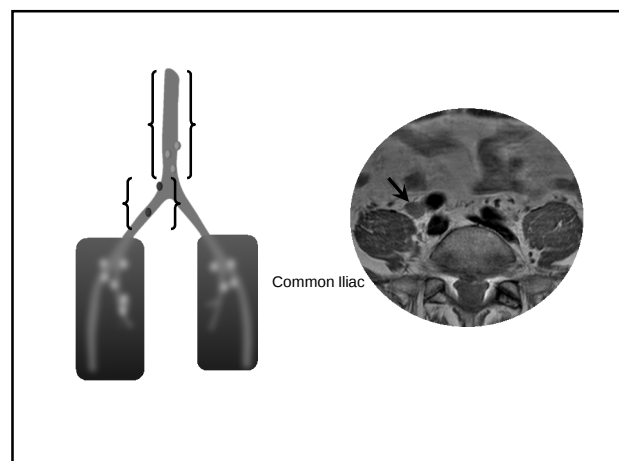
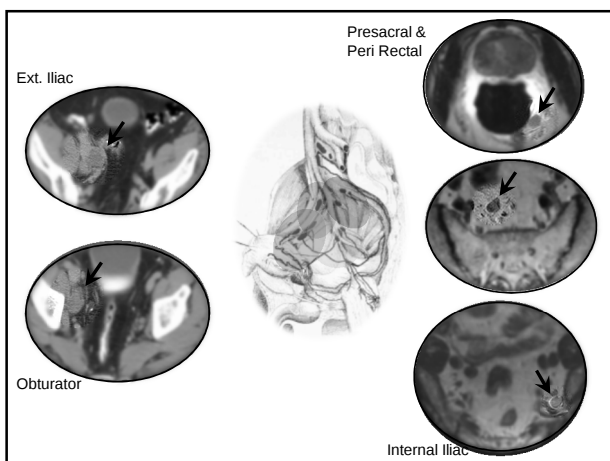
Lymph Node Staging

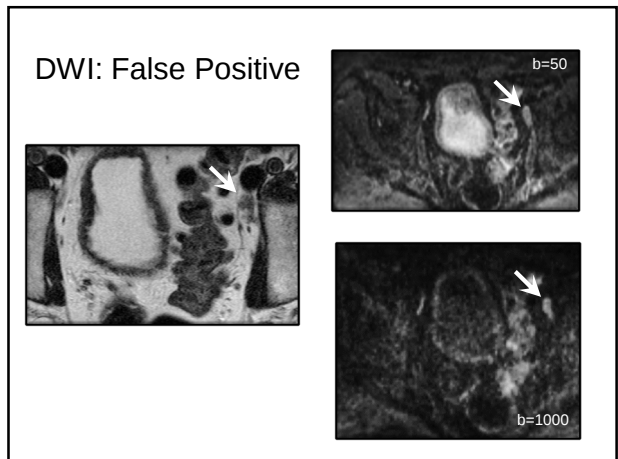
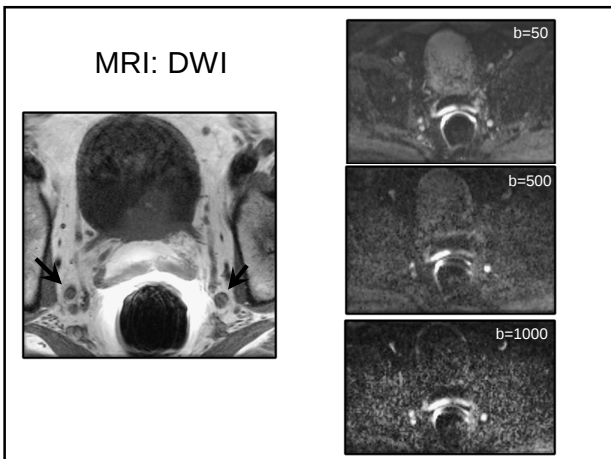
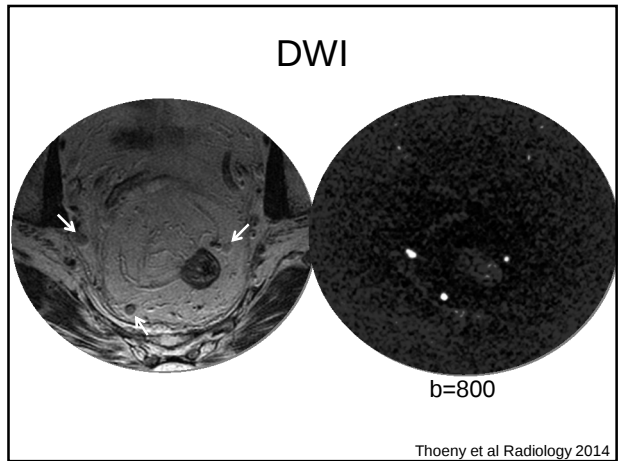
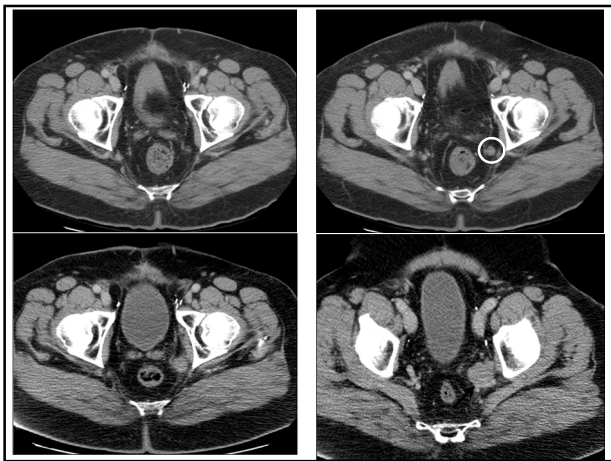
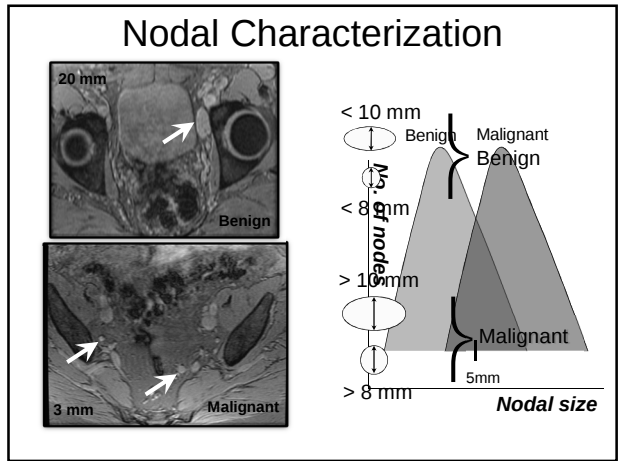
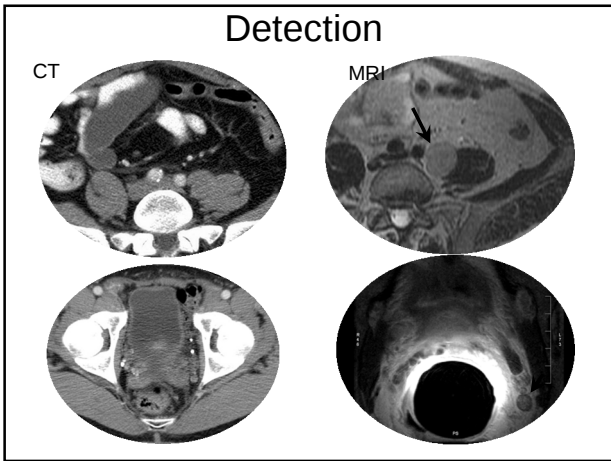
- Achilles heel → imaging
 - Size and Morphology
- PET and New MR techniques

Lymph Node Staging

- Achilles heel → imaging
 - Size and Morphology
- PET and New MR techniques
- Incidence of PLNM (prostate cancer LN metastases) is increasing in last decade → in men 75 years old or older
- This despite overall decrease in the incidence of prostate cancer → raises concern for an increase in disease severity at presentation in the current era

J Urol. 2018;199(6):1510-7





PET Tracers for Nodal Staging

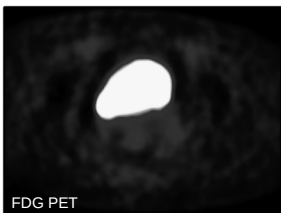
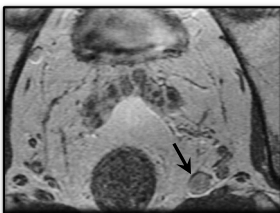
FDG PET

- Low FDG avidity of most prostate cancer cells and urinary activity are suggested as the main limitations of ^{18}F FDG PET in the evaluation of patients with prostate cancer

Effert et al. J Urol 1996

PET Imaging

Cancer Agents	Nodal (N) Staging	Tumor (T) Staging	Metastases (M) Staging
Prostate FDG	Not useful	Not useful	Somewhat useful



Potential Prostate Cancer Imaging Methods

PSMA

- 68Ga-PSMA peptides
- 18F-DCFBC (JHU)
- 99Tc-Trolex (Molecular Insight)
- 111In-capromab pendetide (Prostascint)

Amino Acid Transporters

- 18F-FACBC (BED)
- 18F- 94-9392 (Bayer) (L-glutamate derivative)

Fatty Acids

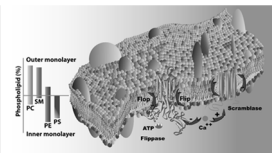
- 11C-Acetate
- 11C-Choline
- 18F-Fluorocholine
- 123I-BMIPP

Others

- Androgen receptors
- NaF bone
- Bombesin
- RGD integrins
- FLT
- FDG

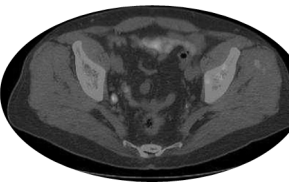
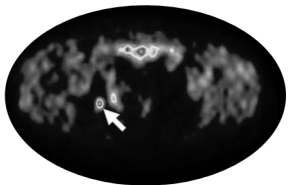
Courtesy Umar Mahmood

[^{11}C] Choline PET



Component of membrane phospholipid

[^{11}C]choline-PET/CT
Sensitivity 64 %; Specificity 90 %
PPV 86 %; NPV 72 %
Accuracy 77%

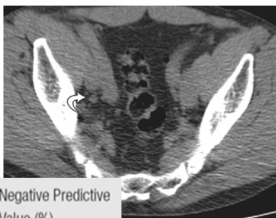
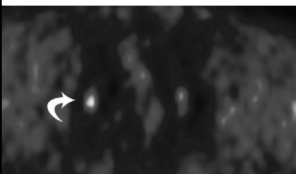


Scattoni et al; European Urology 2007

Performance of FCH PET/CT in the Detection of Malignant LNs

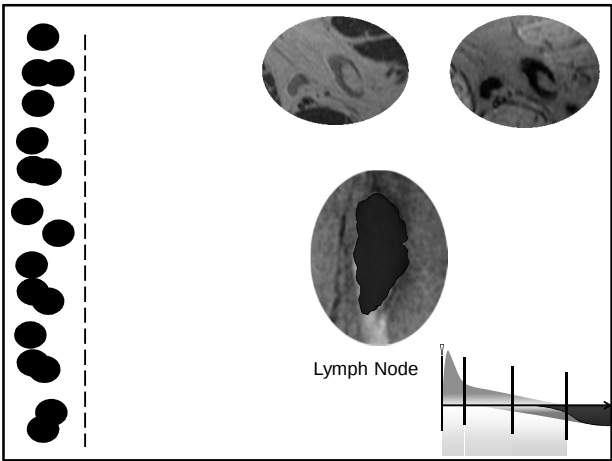
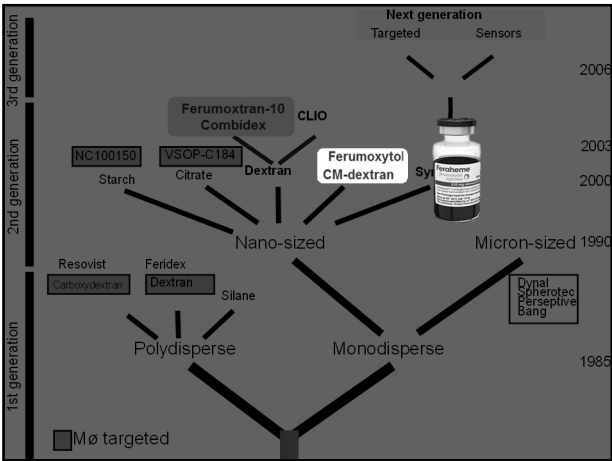
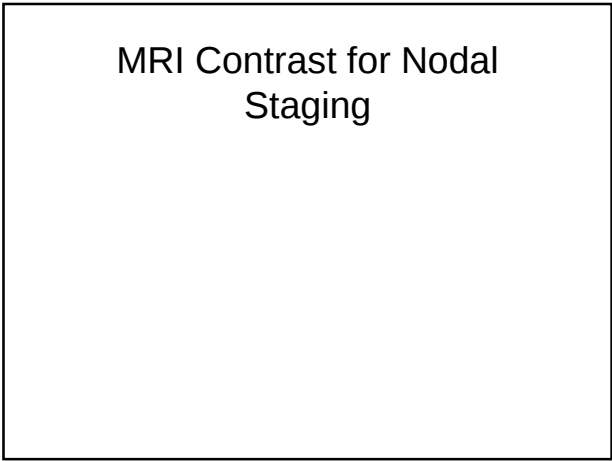
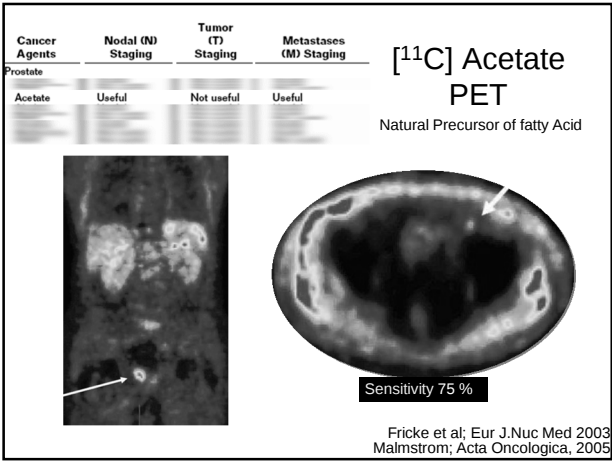
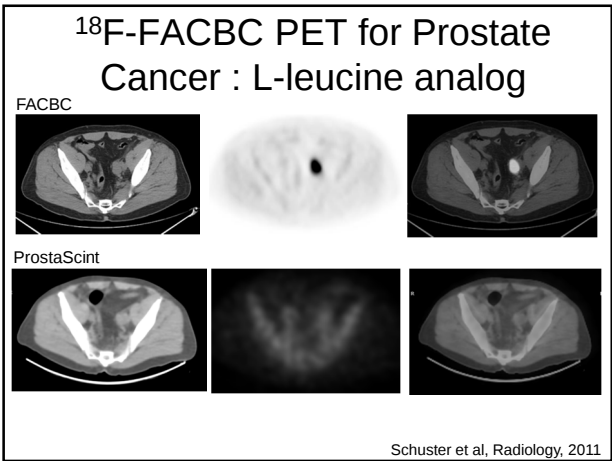
LN Diameter	Total No. of Findings	No. of True-Positive Findings	No. of True-Negative Findings	No. of False-Negative Findings	No. of False-Positive Findings	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
≥5.0 mm	130	18	99	9	4	66	96	82	92
Overall	130	18	86	22	4	45	96	82	83

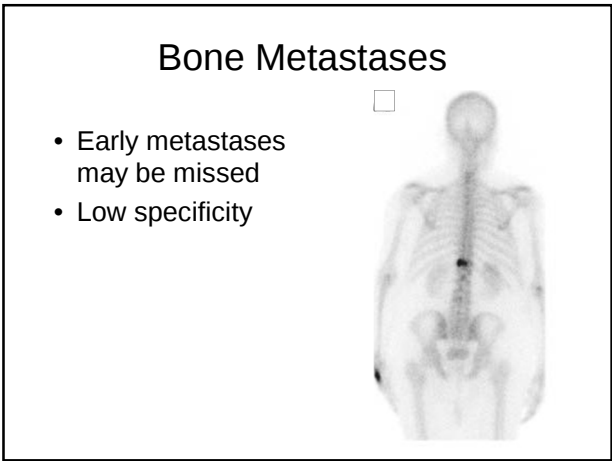
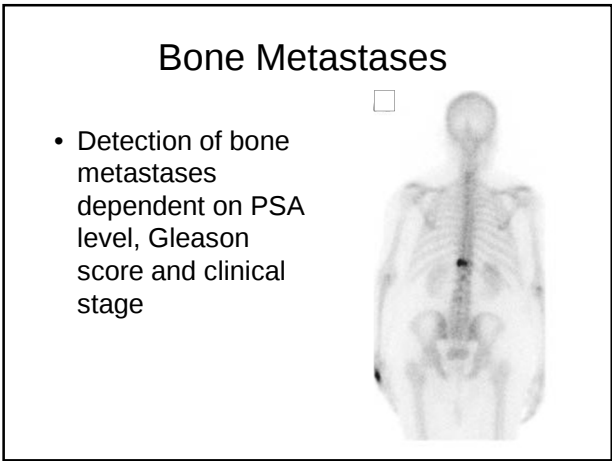
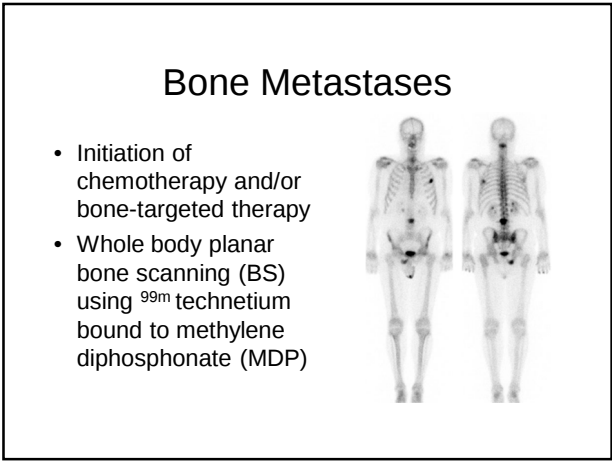
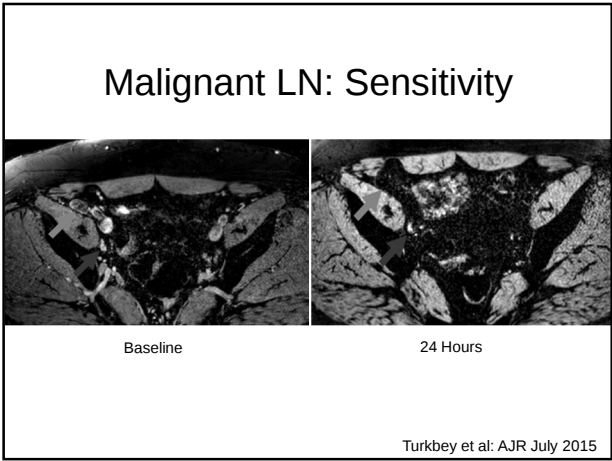
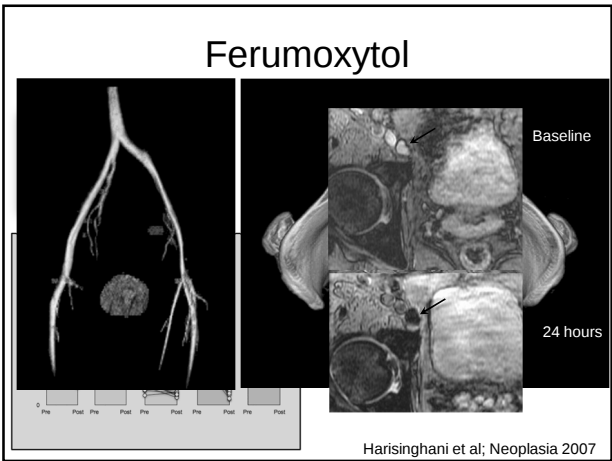
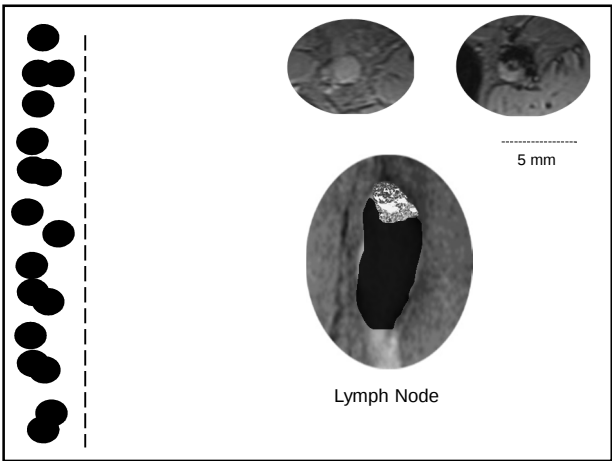
Note.—Overall refers to all malignant LNs, including micrometastases.

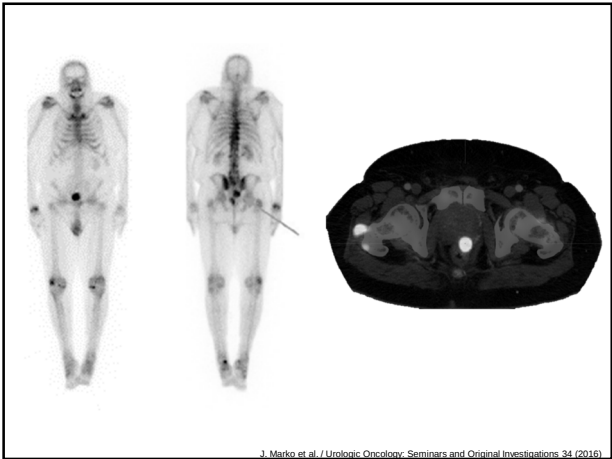


Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)		Negative Predictive Value (%)	
		Value (%)	Value (%)	Value (%)	Value (%)
66	96	82	92	> 5mm	
45	96	82	83	Overall	

Am J Nucl Med Mol Imaging 2015





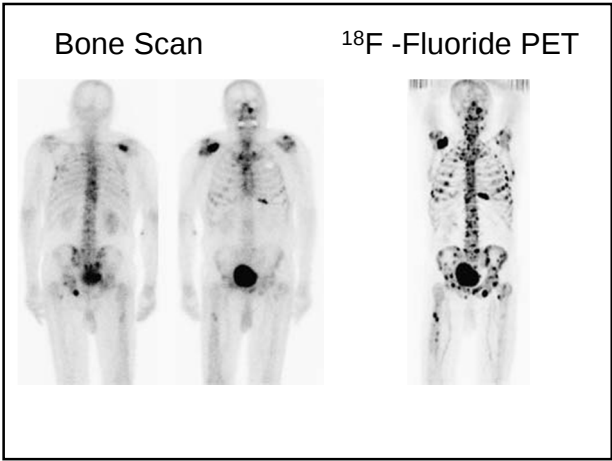


J. Marko et al. / Urologic Oncology: Seminars and Original Investigations 34 (2016)

Bony Metastases

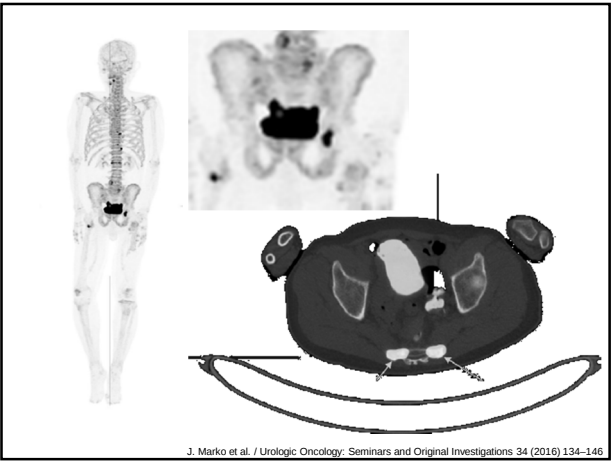
- ^{18}F -Fluoride PET imaging → high sensitivity for detecting bone metastases
- Mechanism
 - increase in regional blood flow
 - Increase bone turnover
- Lower protein binding than MDP

Even-Sapir et al. J Nucl Med 2006;47:287-297



Bone Scan

^{18}F -Fluoride PET

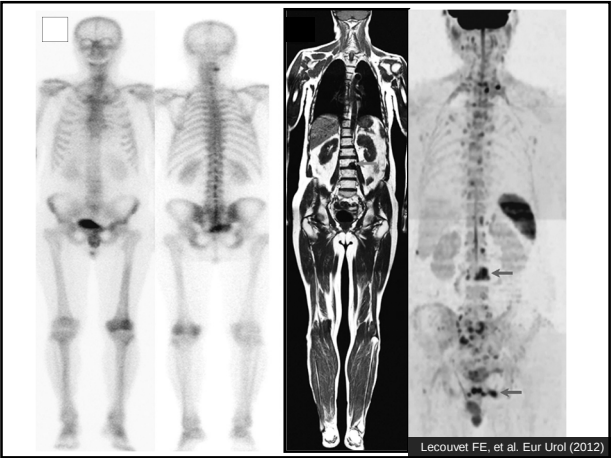


J. Marko et al. / Urologic Oncology: Seminars and Original Investigations 34 (2016) 134–146

TABLE 5
Assessment of Skeletal Metastatic Spread by Planar $^{99\text{m}}\text{Tc}$ -MDP BS, Planar and SPECT BS, ^{18}F -Fluoride PET, and ^{18}F -Fluoride PET/CT: Lesion-Based Analysis of 156 Lesions

Modality	Final diagnosis						Interpretation*			
	Metastases (n = 57)			No metastases (n = 99)			Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	M	E	B/N	M	E	B/N				
Planar BS	13	9	35	2	15	82	39 (23)	83 (98)	56 (87)	70 (69)
Planar and SPECT†	12	23	22	3	10	86	61 (21)	87 (97)	73 (80)	80 (81)
^{18}F -Fluoride PET	19	38	0	3	18	78	100 (33)	79 (96)	73 (86)	100 (100)
^{18}F -Fluoride PET/CT	46	11	0	0	0	99	100 (81)	100 (100)	100 (100)	100 (99)

Even-Sapir et al. J Nucl Med 2006;47:287-297



Lecouvet FE, et al. Eur Urol (2012)

Is BS the best test?

* Reference image	Sensitivity	Specificity	Accuracy	AUC
BS	62 (p < 0.001)	98 (p = 0.32)	90	0.80 (p < 0.001)
SPECT	74 (p < 0.01)	94 (p < 0.01)	89	0.83 (p < 0.01)
SPECT/CT	85 (p = 0.05)	99 (p = 0.32)	96	0.92 (p = 0.24)
PET/CT	93 (*)	99 (*)	98	0.96 (*)
wbMRI+DWI	91 (p = 0.65)	99 (p = 0.32)	97	0.95 (p = 0.92)

Jambor et al Acta Oncol 2015; Epub.

Take Home Points

- Conventional Imaging limited in ability to stage nodes
 - LNMRI and emerging PET tracers will add value
- BS standard of practice of bony metastases
 - Small lesions and specificity
 - Sodium Fluoride PET and Choline PET

Prostate MRI for Evaluation of Prostate Cancer: An Overview of Techniques and Interpretation

Leo L. Tsai, MD PhD MSc
Director of Oncologic Imaging
Director of Genitourinary Imaging
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA



No Relevant Disclosures

Outline

- Equipment
- Pulse Sequences
- Prostate Cancer Detection
 - PI-RADS
- Prostate Cancer Staging

Equipment: 1.5 T vs 3.0 T systems

- 3.0 T is preferred
 - Improved signal/resolution
- 1.5 T systems may offer more open designs
- < 1.5 T is not recommended



Equipment: Endorectal coil

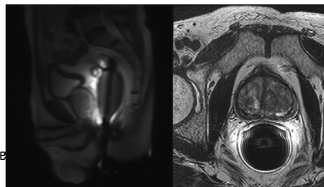
Advantages

- Provides signal boost
- Can improve resolution
- May be required for 1.5 T

Disadvantages

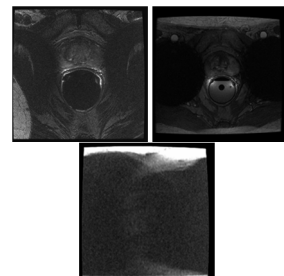
- Discomfort (coil + prone position)
- Workflow
- Distortion may preclude mapping for US fusion or radiotherapy

(coil + prone)



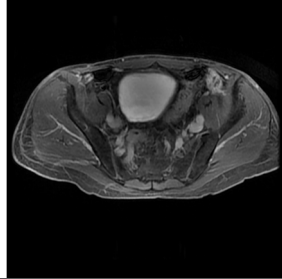
Technical and Safety Considerations

- Patient size
- Implants
 - Hip Replacement
 - Pacemakers
- Claustrophobia
- IV contrast



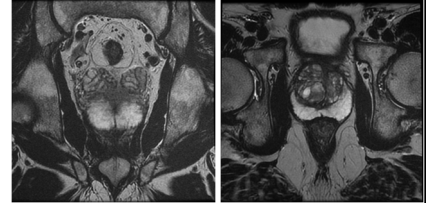
MRI protocol

- Protocols can vary
- Minimum Imaging:
 - T2-Weighted Sequence
 - Diffusion Weighted Imaging
 - Apparent Diffusion Coefficient Map
- Other Sequences:
 - T1-Weighted sequence
 - Dynamic Contrast Enhancement
 - MRI Spectroscopy
 - Large field of view pelvis



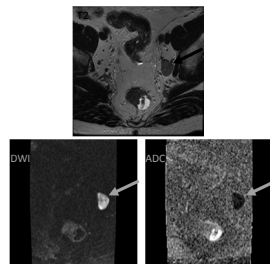
T2 Weighted Sequences

- "Anatomical Sequence"
- T2 hyperintense (bright)
 - Fat (can be suppressed)
 - Fluid
 - Prostate peripheral zone
- T2 hypointense (dark)
 - Fibrosis
 - Dense tissues
 - Calcifications
 - Cortex
 - Tumors



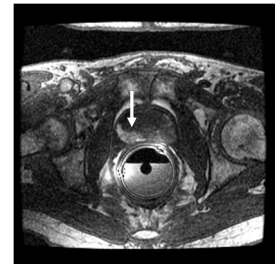
Diffusion Weighted Sequences and ADC

- Detects slow water motion ("restricted diffusion")
- Lesions with high cellularity
- Sensitive for tumors and lymph nodes
- Apparent Diffusion Coefficient (to exclude T2 effect)
- Tumors are DWI "bright", ADC "dark"



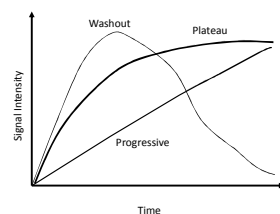
T1 Weighted Sequences

- T1 hyperintense (bright)
 - Blood
 - Fat (can be suppressed)
 - IV Contrast
- T1 hypointense (dark)
 - Fluid
 - Fibrosis
 - Calcifications
 - Cortex



Dynamic Contrast Enhancement

- Pre- and post-contrast images obtained
- Multiple phases obtained
- Focus on arterial enhancement and delayed venous phases
- Tumors: arterial hyperenhancement with venous washout



Prostate Imaging – Reporting and Data System (PI-RADS, version 2, 2015)

- PIRADS 1 – Very low (clinically significant cancer* is highly unlikely to be present)
- PIRADS 2 – Low
- PIRADS 3 – Intermediate (equivocal)
- PIRADS 4 – High
- PIRADS 5 – Very high (highly likely to be present)
- *Gleason score ≥ 7 (including 3+4 with prominent but not predominant Gleason 4 component), and/or volume ≥ 0.5 cc, and/or extra prostatic extension (EPE)

PI-RADS scoring

- Separate scoring for peripheral vs transitional zone tumors
- Peripheral zone lesions- restricted diffusion >> T2 characteristics
- Transitional zone lesions- T2 characteristics >> restricted diffusion
- DCE used for PI-RADS 3 vs 4

<https://www.acr.org/-/media/ACR/Files/RADS/PI-RADS/PIRADS-V2.pdf>

Peripheral Zone (PZ)				
Score	DWI	T2W	DCE	PI-RADS
1	Any*	Any	Any	1
2	Any	Any	Any	2
3	Any	-	Any	3
4	Any	Any	+	4
5	Any	Any	Any	5

Transition Zone (TZ)				
Score	T2W	DWI	DCE	PI-RADS
1	Any*	Any	Any	1
2	Any	Any	Any	2
3	Any	5	Any	3
4	Any	Any	Any	4
5	Any	Any	Any	5

Peripheral Zone Tumors

Assessment of Diffusion

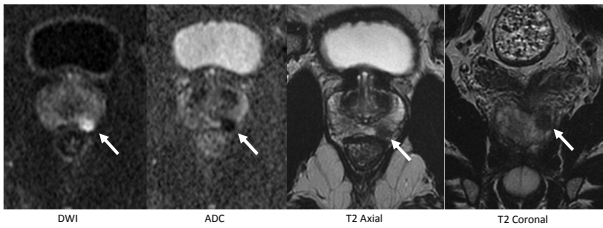
Score	Peripheral Zone (PZ) or Transition Zone (TZ)
1	No abnormality (i.e., normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI
4	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI: <1.5cm in greatest dimension
5	Same as 4, but >1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

More discrete PZ nodules on T2-weighted sequences are more suspicious

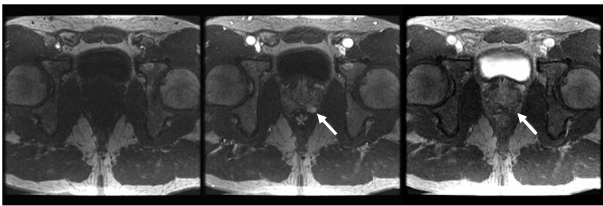
Peripheral Zone (PZ)				
Score	DWI	T2W	DCE	PI-RADS
1	Any*	Any	Any	1
2	Any	Any	Any	2
3	Any	-	Any	3
4	Any	Any	+	4
5	Any	Any	Any	5

<https://www.acr.org/-/media/ACR/Files/RADS/PI-RADS/PIRADS-V2.pdf>

Example: PI-RADS 4 PZ Lesion



DCE Washout Kinetics



Transitional Zone Tumors

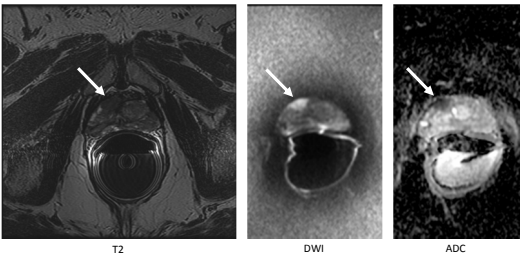
T2 Scoring for Transition zone

Score	Transition Zone (TZ)
1	Homogeneous intermediate signal intensity (normal)
2	Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)
3	Heterogeneous signal intensity with obscured margins Includes others that do not qualify as 2, 4, or 5
4	Lenticular or non-circumscribed, homogeneous, moderately hypointense, and <1.5cm in greatest dimension
5	Same as 4, but >1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

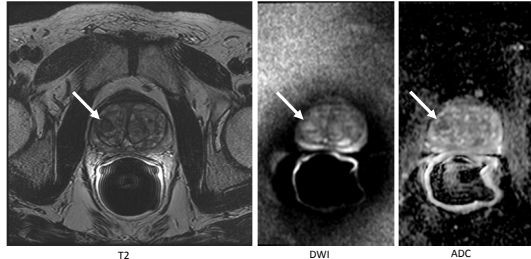
Less discrete TZ nodules on T2-weighted sequences are more suspicious

Transition Zone (TZ)				
Score	T2W	DWI	DCE	PI-RADS
1	Any*	Any	Any	1
2	Any	Any	Any	2
3	Any	5	Any	3
4	Any	Any	Any	4
5	Any	Any	Any	5

Example: PI-RADS 4 TZ Lesion

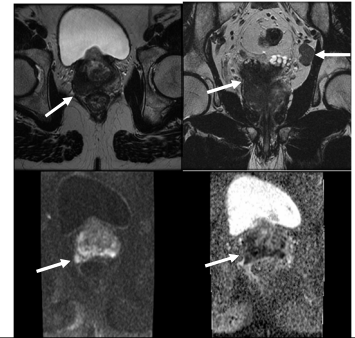


Example: BPH Nodule



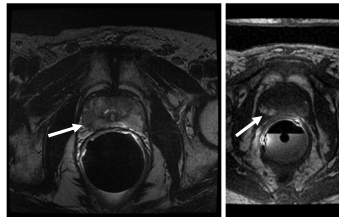
Staging

- Look for extraprostatic extension
- Capsular bulging
- Neurovascular contact/encasement
- Lymphadenopathy
- Post-contrast images can be helpful



Pitfalls

- Exophytic BPH nodules
- Stromal Tissue
- Prostatitis
- Hemorrhage
- Post-treatment changes



Summary

- MRI equipment and techniques can vary from site to site
- Pulse sequence design is as important as equipment
- Be aware of potential technical limitations
- Peripheral and transitional zone tumors are detected differently
- PI-RADS template is now widely accepted
- Talk to your radiologists!

Scrotal Ultrasound

Aoife Kilcoyne, MB BCH BAO

Disclosures

- I have no disclosures

Learning Objectives

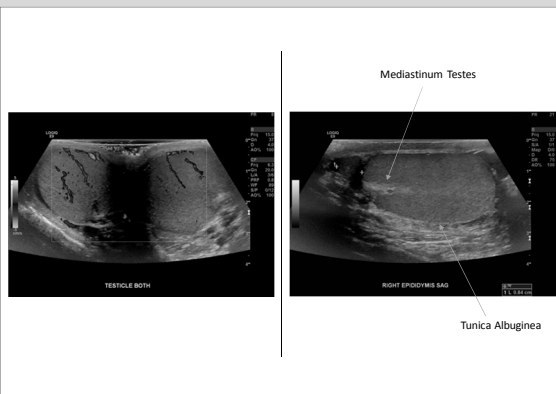
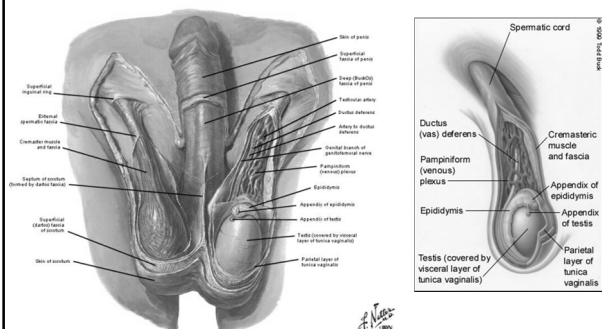
- US technique
- Normal anatomy
- Acute
 - Testicular torsion
 - Epididymo-orchitis
- Non acute
 - Varicocele
 - Testicular masses: benign/malignant
 - Extra-testicular masses

Technique

- Supine position
- High resolution transducer – 10-14 Mhz
- Supine patient
- Legs slightly apart
- Towel under testes
- Images: transverse, sagittal images – testes, epididymis, both testes color Doppler, pulsed wave Doppler

Normal Anatomy

Scrotum and Contents
Anterior View



Contents of Spermatic Cord

- Testicular artery
- Testicular veins (pampiniform plexus)
- Testicular lymph vessels
- Autonomic nerves
- Remains of processus vaginalis
- Vas deferens
- Cremasteric artery (branch of the inferior epigastric)
- Artery of vas deferens (branch of inferior vesical)
- Genital branch of genitofemoral nerve (L1-L2)

Blood Supply of the Testis

- Testicular artery originates from aorta
- Deferential artery originates from the superior vesical artery
- Cremasteric artery originates from inferior epigastric artery

Normal Structures

- Mediastinum testis
- Hypoechoic band
- Rete testis



Tumors and Tumorlike Lesions of the Testis:
Radiologic-Pathologic Correlation. Paula J.
Woodward, MD, Roya Sohani, MD, Michael J.
O'Donoghue, LCDR, MC USNR and Douglas E. Green,
MD Radiographics. 2002;22:1899-216.

Acute

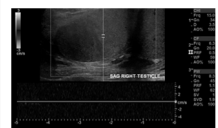
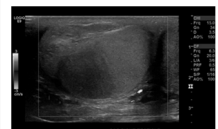
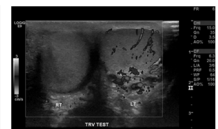
Testicular Torsion

- Surgical emergency
 - Surgery within:
 - 6 hours – 80% salvage
 - 12 hours – 70% salvage
 - > 12 hours – 20% salvage
 - Etiology
 - Bell clapper anomaly



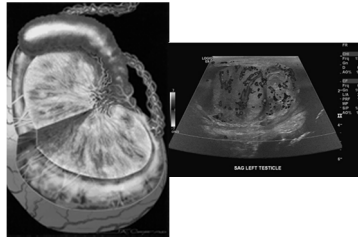
Testicular Torsion

- US findings < 6 hours
 - Hypoechoic, enlarged testis
 - Lack of detectable/attenuated Color Doppler flow
 - PW Doppler asymmetry in subtle cases, tardus parvus
- > 6 hours – 10 days
 - Progressive enlargement, hydroceles, heterogeneous
 - Pitfalls
 - Detorsion with hyperemia – painful at scan time?



Epididymitis and epididymo-orchitis

- Most common cause of the "acute scrotum"
- Young men: GC, Chlamydia
- Older men: G -ve organisms
- Mumps - uncommon
- US findings: enlargement, hypoechoic, hyperemic. Orchitis – begins adjacent to epididymis, spreads



Medical illustration by James A. Cooper, MD, Radiology Medical Group, San Diego, California (Radiographics. 2003;23:214.)

Avery et al, Radiographics, 2013

Non-Acute

Scrotal Mass

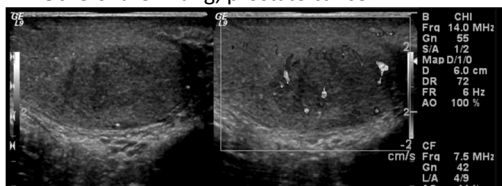
- Decision:
 - Intratesticular or extratesticular
- Intratesticular
 - Most cancers are hypoechoic. But necrosis, hemorrhage can produce hyperechoic foci
 - Sonographic appearance not specific
 - All intratesticular masses should be considered malignant until proven otherwise

Scrotal Mass Contd.

- Ultrasound is highly sensitive for detection of intratesticular masses ~98%
- Primary testicular neoplasms
 - ~ 95% germ cell tumors – most malignant
 - Seminoma 50%
 - Embryonal cell carcinoma 25%
 - Teratomas 10%
 - Choriocarcinoma 3%
 - Yolk sac tumors (60% in infants)
 - ~ 5% stromal – Sertoli or Leydig cell tumor – most benign

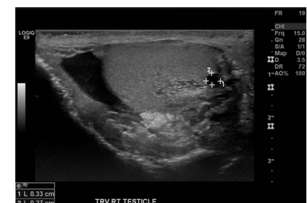
Scrotal Mass Contd.

- Secondary testicular neoplasms
 - Lymphoma (especially older men)
 - The most common bilateral testicular tumor
 - Leukemia (sanctuary site)
 - Others rare – lung, prostate cancer



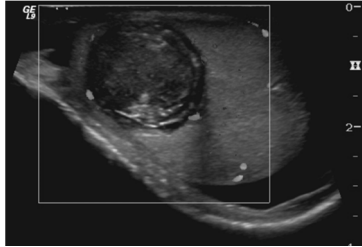
Benign Testicular Masses

- Tunica albuginea cysts – peripheral, 2-5 mm, simple
- Ectasia of the rete testis



Benign Testicular Masses

- Epidermoid cyst
 - Layered appearance
 - Not entirely specific
 - Imaging may prompt testicle-sparing surgery esp. in setting of infertility



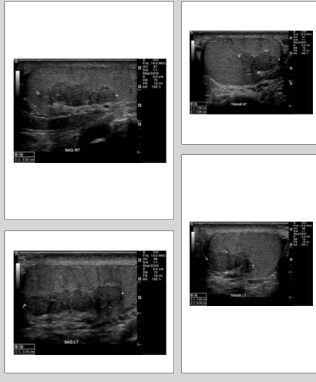
Benign Testicular Masses

- Testicular abscess
 - Irregular
 - Increased through transmission of sound
 - Peripheral hyperemia
 - +/- skin thickening



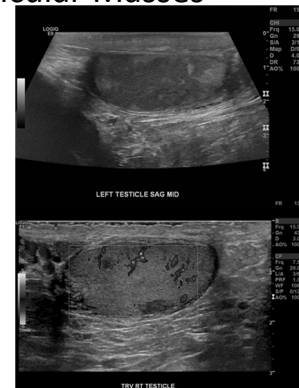
Benign Testicular Masses

- Adrenal rests
 - Adrenal tissue present in 1.6% of adult testes and ~10% of neonates
 - In congenital adrenal hyperplasia or Cushing syndrome, adrenal rest hyperplasia may produce benign masses



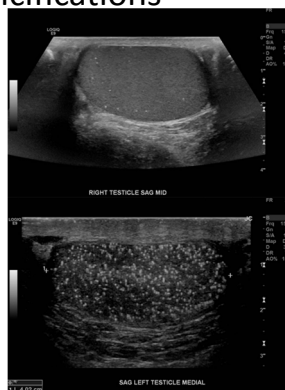
Benign Testicular Masses

- Testicular Infarction
 - Torsion, trauma, emboli, vasculitis, sickle cell disease, leukemia
 - Well defined, avascular, painful
 - Can confirm with MRI
 - urology referral, close observation mandatory
- Sarcoid



Testicular Calcifications

- Testicular microlithiasis
 - Etiology unknown
 - Associated with germ cell tumors
 - Value of follow up imaging questionable, variably followed up at different institutions.

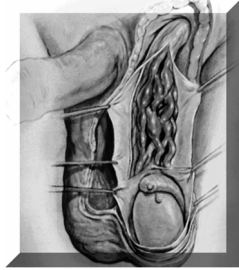


Testicular Calcifications

- Coarse calcifications
 - Dystrophic
 - Calcified hematoma
 - Burnt out tumor
 - Sertoli cell tumor – large cell variant, echogenic masses

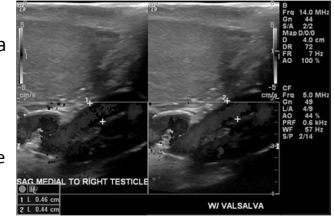
Varicocele

- Abnormal dilation of the veins of the pampiniform plexus
 - Primary (idiopathic)
 - Secondary (proximal obstruction)
 - New varicocele in a patient > 40 years warrants CT abdomen



Varicocele

- Three grades (clinical)
 - 1 – palpable with Valsalva
 - 2 – without Valsalva
 - 3 – Visible
- US criteria
 - Multiple veins (? > 3)
 - > 3mm, but > 5 mm more likely significant
 - Reversal of flow after Valsalva – prolonged reversal (> 2 sec) significant
 - Short reversal (< 1 sec) physiologic



Varicocele

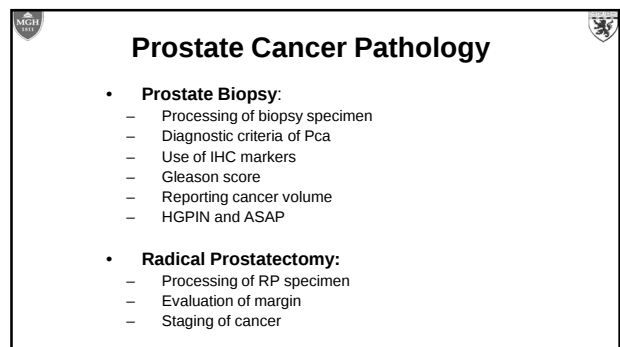
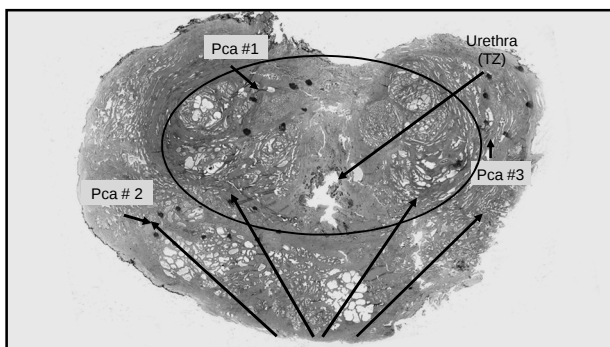
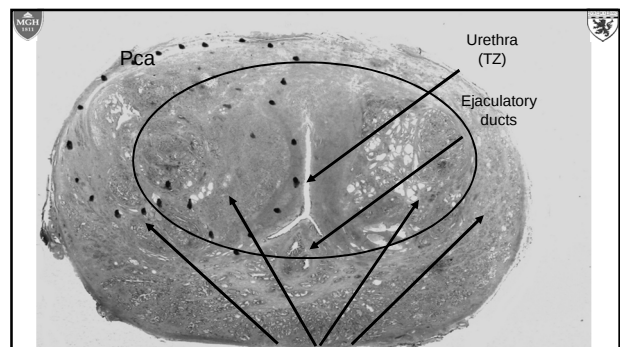
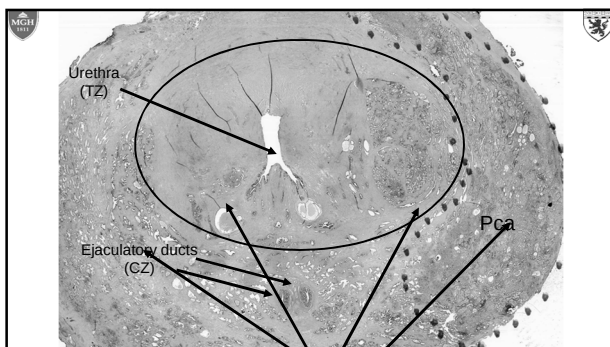
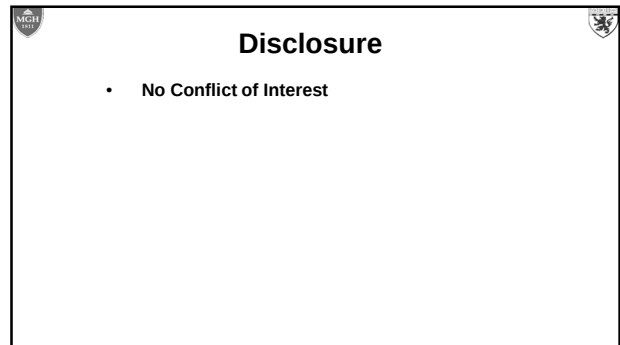
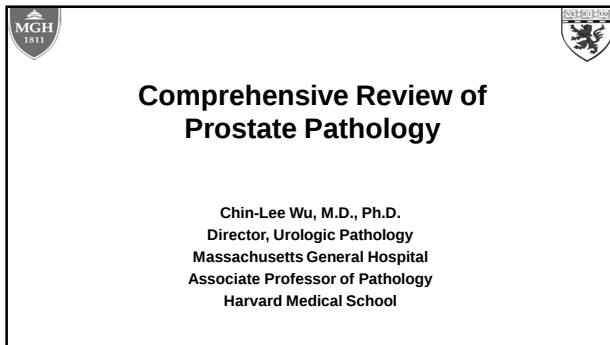
- **Fertile** asymptomatic men – clinical varicocele present in up to 15% and reversed flow with Valsalva in 25%
- Varicocele is a major contributor to male infertility but sonographic findings do not correlate well with severity of disease

Extratesticular Mass

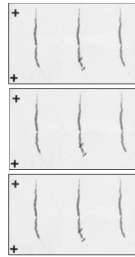
- Benign more common
- Lipoma most common
- Fat
 - Lipoma, liposarcoma, angiomyofibroblastoma (AMF)
- Enhancing soft tissue + fat:
 - Liposarcoma, AMF
- Fibrous
 - Fibrous pseudotumor

Wolfman et al, *Radiographics*, 2015

Thank you



Standard Prostate Biopsy

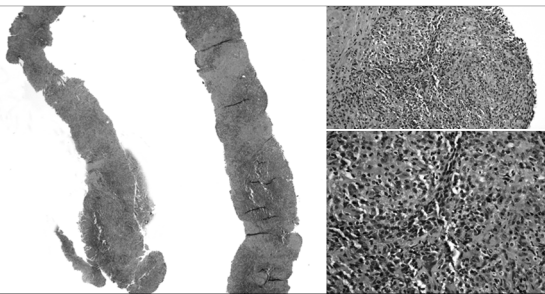


- Level 1, H&E
- Level 2, Unstained Blank for IHC
- Level 3, H&E

Prostate Biopsy Diagnosis

- Benign Prostatic Tissue, 65%
 - BPH: Not diagnosed on biopsy
 - Inflammation/Prostatitis
- Adenocarcinoma, 25-30%
- High Grade PIN, 5%
- Atypical Small Acinar Proliferation (ASAP), 2%

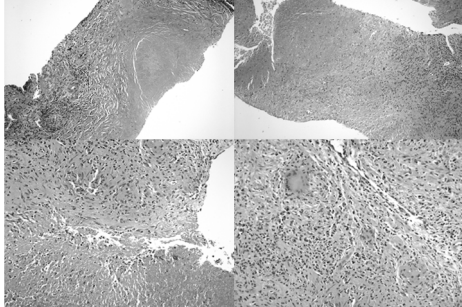
Nonspecific Granulomatous Prostatitis



Nonspecific Granulomatous Prostatitis

- Most common form of granulomatous prostatitis
 - Followed by post-bx prostatitis and BCG prostatitis
- Etiology: Reaction to bacterial toxin, secretion
- Median age: 62 yrs
- Symptoms: irritable or obstructive voiding etc
- DRE: Indurated, similar to Pca
- Associated with elevated PSA
- Abnormal DRE may persist 2-8 yrs

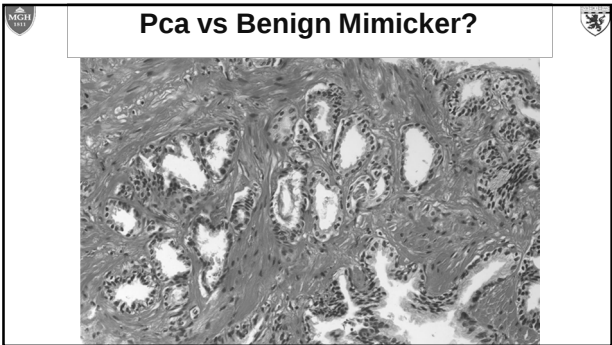
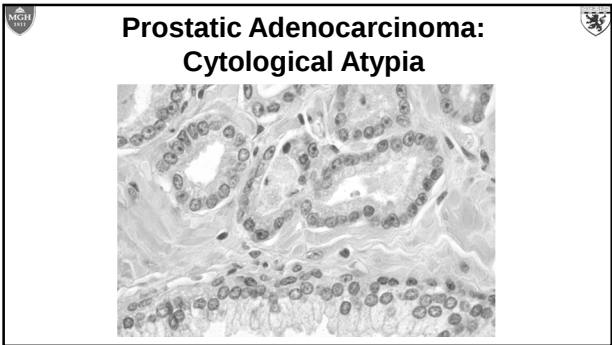
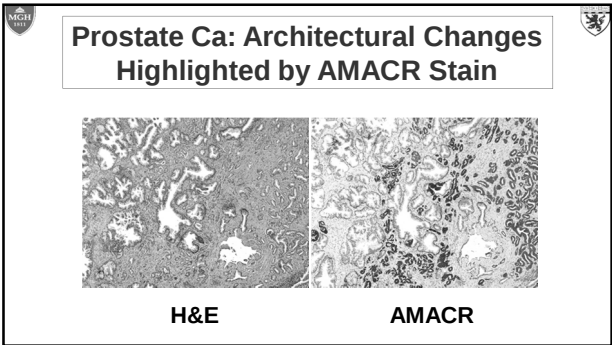
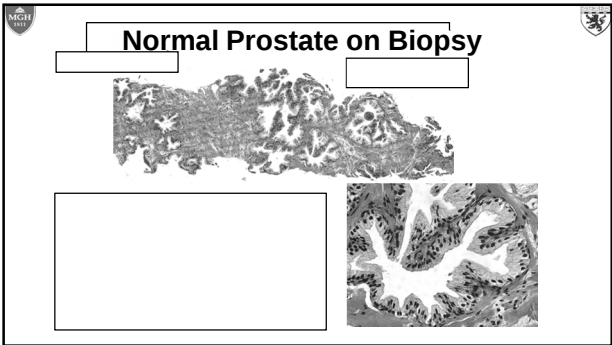
BCG Necrotizing Granulomatous Prostatitis



Prostatic Adenocarcinoma: Primary Criteria defined in 1953

- Architectural Atypia
- Cytologic Atypia
- Lack of Basal Cells

• Totten, R. S., N. W. Heinemann, P. B. Hudson, E. E. Sproul, and A. P. Stout. Microscopic differential diagnosis of latent carcinoma of the prostate. Arch Pathol Lab Med 1953. 55:131-141.



Primary Criteria for Cancer:

- Architectural Atypia
- Cytologic Atypia
- Lack of Basal Cells

Immunological Profile of PCa

- Negative for Basal Cell Markers
 - p63, 34bE12
- Over-expression of AMACR/P504S

Prostatic Adenocarcinoma: Immunohistochemical Profiles

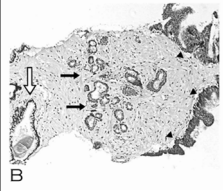
Diagnosis	(Basal Cell) 34bE12 /p63	AMACR
Benign	P	N
Prostate Cancer	N	P

MGH

MIT

Triple Antibody Stain

BenignPcaHGPIN



34βE12-p63
Mouse McAbs
Detected with DAP (Brown)

AMACR
Rabbit McAb
Detected with AEC (Red)

MGH

MIT

High Grade Prostatic Intraepithelial Neoplasia (HGPIN)

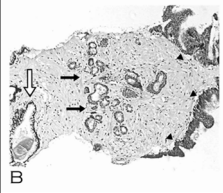
Do not report low grade PIN
Precursor to adenocarcinoma
Some are associated with concurrent adenocarcinoma
33% re-biopsy positive for cancer
50% re-biopsy positive when 4 or more cores HGPIN are present

MGH

MIT

Triple Antibody Stain

BenignPcaHGPIN



34βE12-p63
Mouse McAbs
Detected with DAP (Brown)

AMACR
Rabbit McAb
Detected with AEC (Red)

MGH

MIT

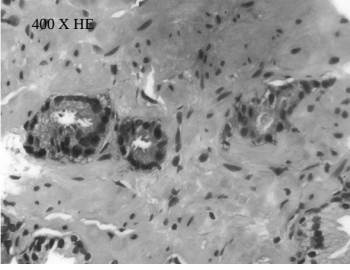
Pca and HGPIN: Immunohistochemical Profiles

Diagnosis	34βE12 /p63	AMACR
Benign	+++	-
HGPIN	++	++
Prostate Cancer	-	+++

MGH

MIT

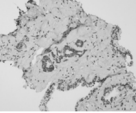
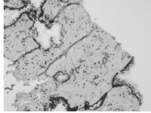
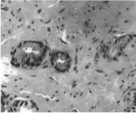
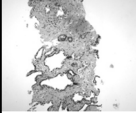
Small Focus of Atypical Glands



MGH

MIT

Atypical Small Acinar Proliferation (ASAP)



100 X HE400 X HE34βE12AMACR

Not 100% sure it is cancer. Recommend rebiopsy.

Pathologic Findings in Determining Eligibility for Active Surveillance Consensus and Recommendation from CAP, ISUP, ADASP, NZSP and PCF

CAP: College of American Pathologists
ISUP: International Society of Urologic Pathology
ADASP: Asso. of Directors of Anatomical and SP
NZSP: New Zealand Society of Pathology
PCF: Prostate Cancer Foundation

Amin, MB et al Arch Pathol Lab Med. 2014; 138:1387-1405

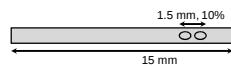
Reporting of Positive Biopsy Cores for Active Surveillance

- Histologic Type
- Number of Positive Cores
- Location of Positive Cores
- Tumor Quantification (% or mm)
- Gleason Scores
- ASAP on Separate Cores
- Other Findings (report only if present):
 - Extraprostatic Extension (EPE)
 - Perineural Invasion (PNI)

Amin, MB et al Arch Pathol Lab Med. 2014; 138:1387-1405

Tumor Extent on Biopsy Recommendation from CAP, ISUP, ADASP, NZSP and PCF

- # of positive cores / total # of cores
- Linear % of cancer in the involved core (not area)
 - (eg. 10%, comment if core < 6 mm) *and or*
- Linear length mm of cancer and total core length
 - (eg. 1.5 mm involved in a 15 mm core)



Amin, MB et al Arch Pathol Lab Med. 2014; 138:1387-1405

MGH Reporting Format (for each block)

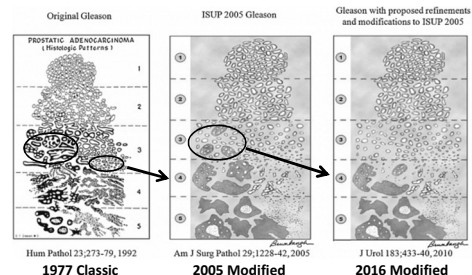
- Prostatic adenocarcinoma
- Gleason Score: 3+3 (Grade group 1)
- Number of cores involved: 2 of 2
- Percentage and length involved by cancer: 10%, 2 mm; <5%, <0.5 mm
- Perineural invasion is: present

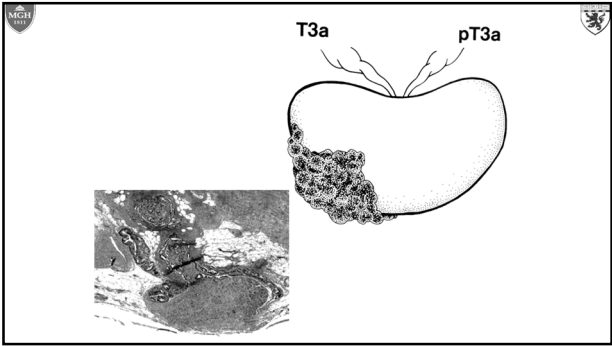
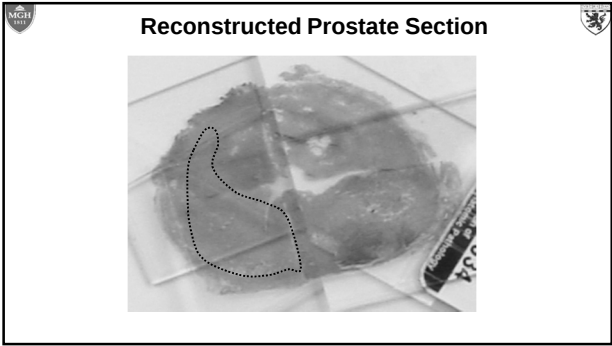
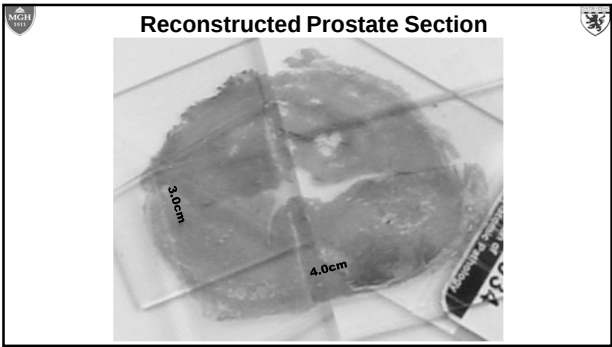
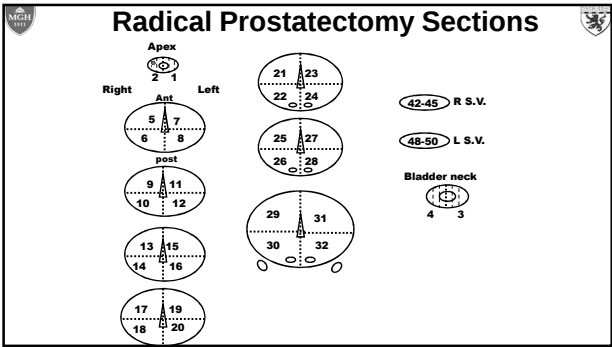
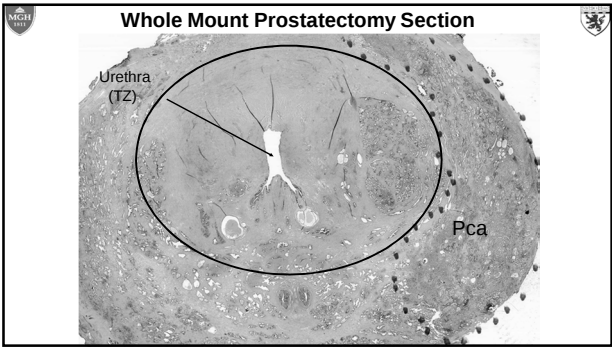
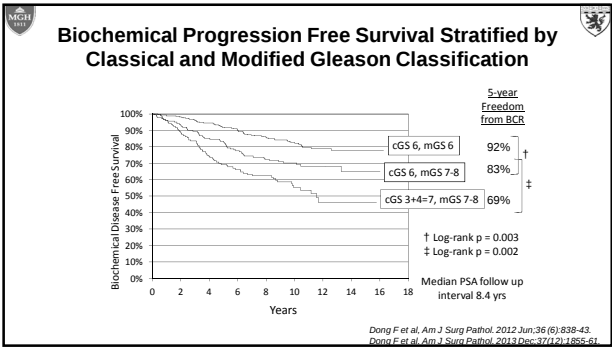
Gleason Grading System

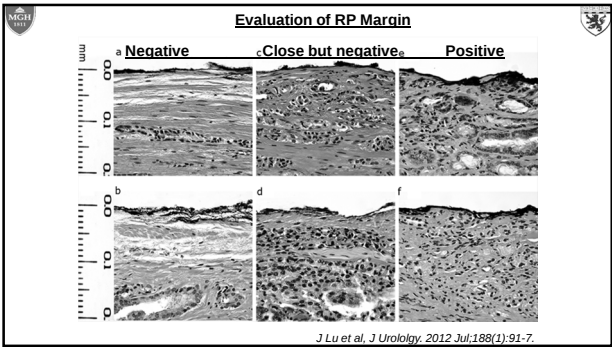
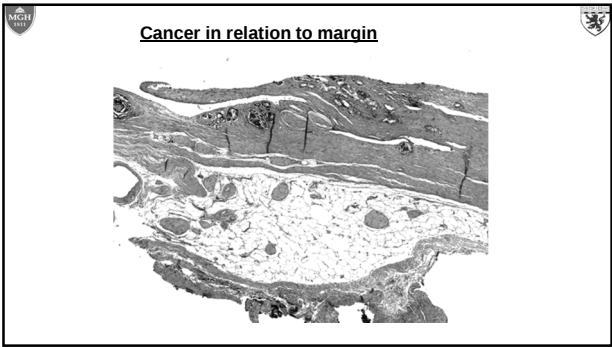
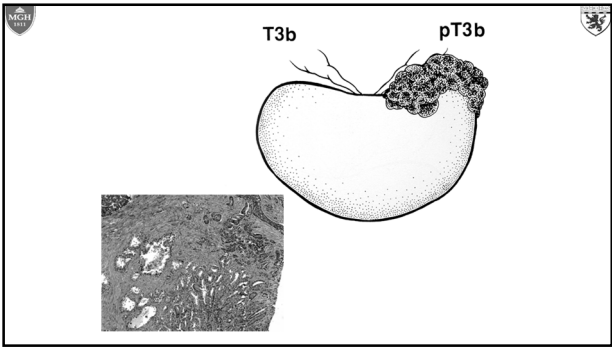
- Created based on correlation between morphological patterns and clinical outcome
- The VACURG studies in 1950-'60'
- Morphologically: emphasis on glandular differentiation in relation to stroma
- Powerful predictor of clinical outcome
- *Not to grade Pca outside prostate (mets, EPE, PNI)*



Gleason Grading System







**Comprehensive Review of
Kidney Tumor Pathology**

Chin-Lee Wu, MD, PhD
Director, Urological Pathology
Massachusetts General Hospital
Associate Professor of Pathology
Harvard Medical School

Tumors of the Kidney (2016 WHO)

- Clear cell renal cell carcinoma (8310/3)
- Papillary renal cell carcinoma (8255/1)
- Chromophobe renal cell carcinoma (8317/3)
- Collecting duct carcinoma (8319/3)
- Renal medullary carcinoma (8510/3)
- Renal cell carcinoma, unclassified (8312/3)
- Papillary adenoma (8260/0)
- Oncocytoma (8290/0)
- Multilocular cystic renal neoplasm of low malignant potential (8316/1)
- Clear cell papillary renal cell carcinoma (8323/1)
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- Succinate dehydrogenase (SDH)-deficient renal carcinoma (8312/3)
- Mucinous tubular and spindle cell carcinoma (8480/3)
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- MIT Family translocation carcinomas (8311/3)
- Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma (8311/3)



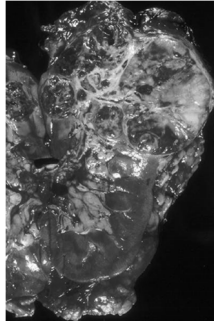
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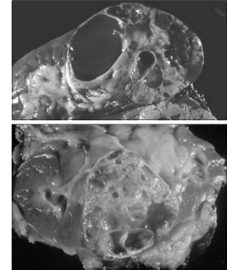
RCC, Clear Cell Type

- Most are solitary
- Multiple often associated with von Hippel-Lindau disease
- Rounded, bosselated
- Non-encapsulated
- Pushing margin
- Golden-orange due to rich lipid content:
 - Cholesterol
 - Neutral lipids
 - Phospholipids
- Associated with necrosis, cystic degeneration, hemorrhage and calcification.



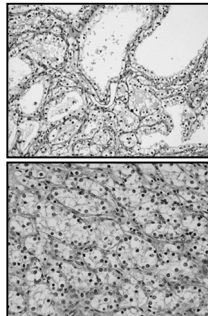
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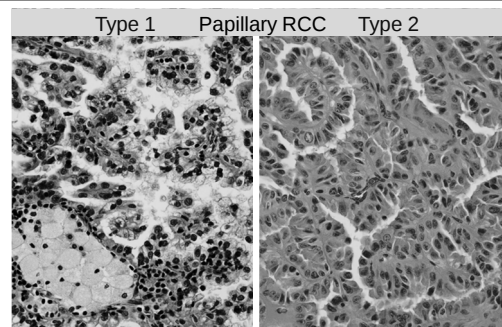
Clear Cell RCC

- Delicate interconnecting vasculature "sinusoidal"
- Compact and tubulocystic architecture
- Clear cytoplasm
- Low nuclear/cytoplasmic ratio
- Can have eosinophilic granular cytoplasm



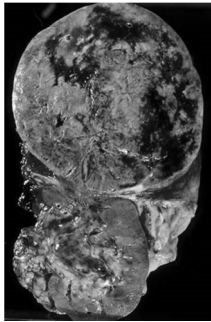
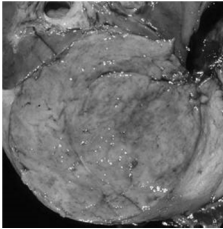
Papillary Renal Cell Carcinoma

Gray-tan
Well circumscribed
2-18 cm (mean 7cm)
75% at poles
40% multiple



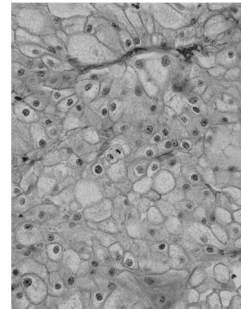
Chromophobe RCC

Gray, beige
Well circumscribed

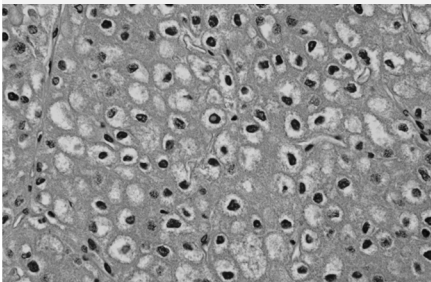


Chromophobe RCC, Conventional Type

- Compact architecture
- Large sheets mosaic pattern
- Large cells
- Prominent cytoplasmic membrane ("plant-like")
- Pale flocculent cytoplasm
- Perinuclear halo
- Wrinkled nuclear contours
- Hyperchromatic nuclei
- Binuclear cells
- Mixed with eosinophilic cells

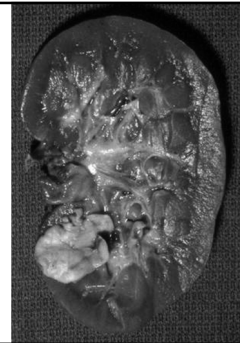


Chromophobe RCC, Eosinophilic Type



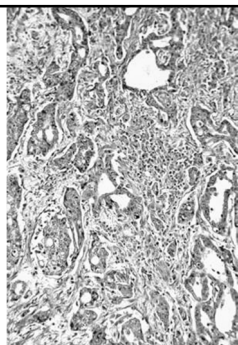
Collecting Duct Carcinoma

- 1-2% of renal tumors
- 2/3 cases symptomatic
- 80% have nodal mets
- Wide age group
- Deep medulla
- Infiltrative borders



Collecting Duct Carcinoma

- Branching tubules
- Desmoplastic stroma, neutrophils
- Cords, papillae, microcysts
- Eosinophilic cells, prominent nucleoli, hobnail, focal mucin
- Dysplasia nearby collecting ducts



Unclassified RCC

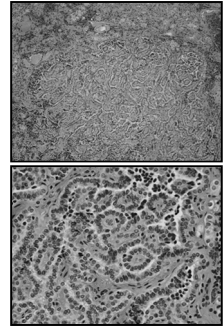
- Not a distinct entity
- Tumors do not fit into any of the recognized entities
- Could be low grade or high grade

Tumors of the Kidney (2016 WHO)

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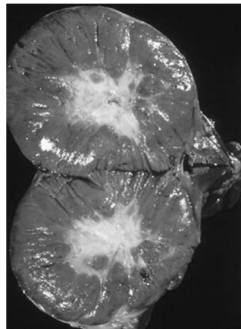
Papillary Adenoma

- Diameter ≤ 1.5 cm (previously 0.5 cm)
- Unencapsulated mass
- Histologically indistinguishable from low grade papillary RCC



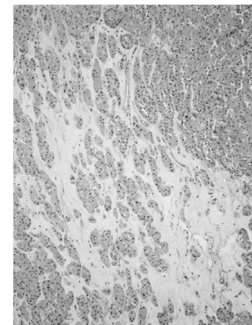
Oncocytoma

- 5-9% of renal tumors
- Mahogany brown
- Well circumscribed
- 50% central stellate myxoid fibrosis
- Some large, >15 cm
- 5% bilateral/multifocal



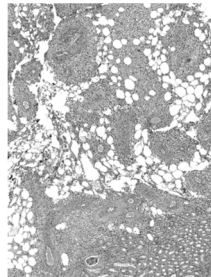
Oncocytoma

- Compact or nested
- Fine granular cytoplasm
- Round, small nuclei
- Often prominent nucleoli
- Nuclear pleomorphism "bizarre cells" in 10%

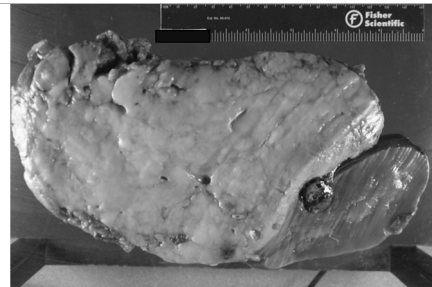


Angiomyolipoma (AML)

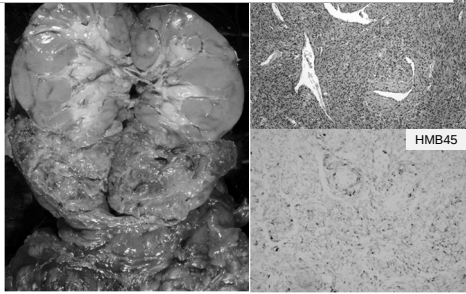
- Hamartoma vs neoplasm
- 3 components:
 - Dysmorphic thick wall blood vessels
 - Spindle smooth muscle cells, can be epithelioid
 - Adipose cells
- Associated with tuberous sclerosis complex (TSC) or sporadic
- Benign, risk of bleeding/rupture
- Cell origin: Perivascular epithelioid cells (PEComas)
- IHC
 - HMB-45+, Melan A +, Vimentin+, Actin+
 - Adipocyte S-100+
 - Keratin-, EMA-



Angiomyolipoma (AML) Fat Rich



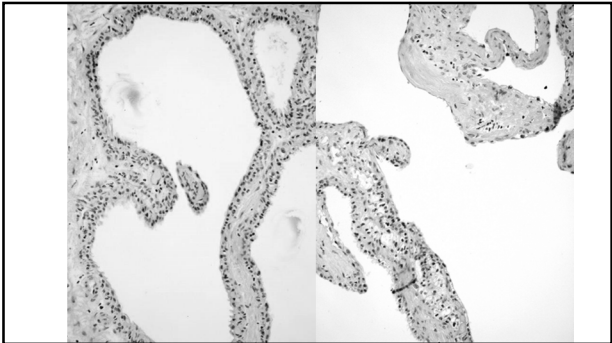
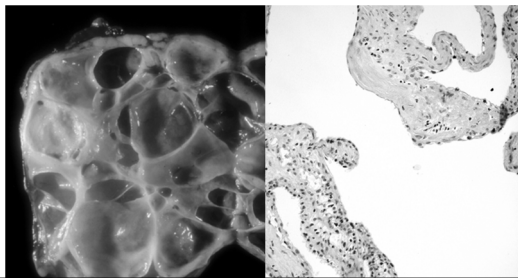
Angiomyolipoma (AML) Fat Poor



Tumors of the Kidney (2016 WHO)

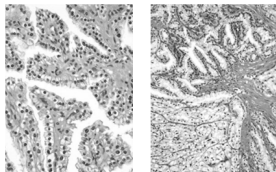
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Multilocular Cystic Renal Neoplasm of Low Malignant Potential (Previously Multilocular Cystic RCC)



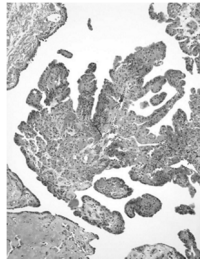
Clear-Cell Papillary RCC

- Adult Population, 1-5% of Renal Tumors
- Indolent Course
- Small (Mean size 2.4 cm)
- Often Cystic with Fibrous Capsule and Stroma
- No Gain of Chrom 7, 17 or Loss of Y (Not PRCC)
- No Del of 3p, VHL Mutations, or VHL Promoter Hypermethylation (Not CC-RCC)



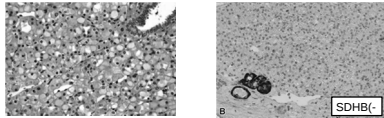
Acquired Cystic Disease (ACD)-Associated RCC

- Most common RCC in end stage kidney disease & acquired cystic disease
 - 36% of dominant mass in end stage kidney diseases
 - 46% of dominant mass in acquired cystic diseases
- Multifocal, bilateral
- Well circumscribed, associated with cysts
- Main features
 - Cribriform, sieve-like structure
 - Eosinophilic cytoplasm (often mistaken for PRCC type 2), Grade 3 nuclei
 - Intratumoral oxalate crystals

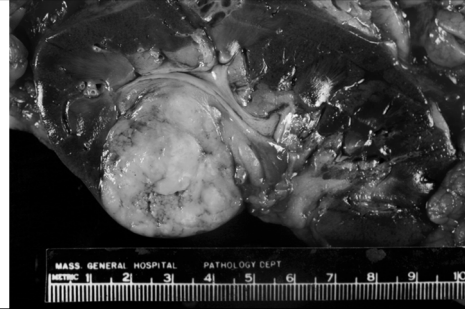


Succinate dehydrogenase (SDH)-deficient RCC

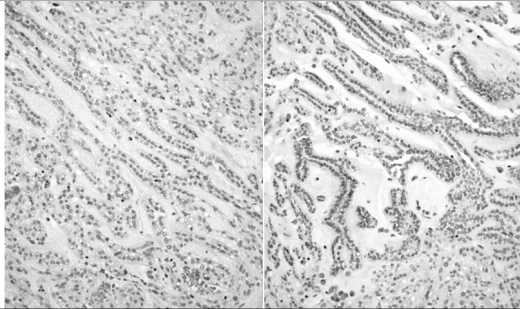
- The most distinctive feature is the presence of **cytoplasmic vacuoles**
- IHC is a useful tool for their diagnosis because there is a loss of expression of SDHB
- It presents mainly in young adults, and most patients have germline mutations in an SDH gene
- Most SDH-deficient RCC has good prognosis



Mucinous Tubular and Spindle-Cell Carcinoma

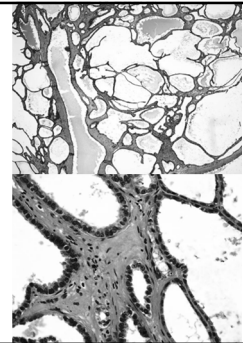


Mucinous Tubular and Spindle-Cell Carcinoma



Tubulocystic RCC

- >90% indolent course
- M:F >7:1
- Incidental complexed cyst on CT
- Sponge-like gross appearance
- Grade 3 nuclear features



Tumors of the Kidney (2016 WHO)

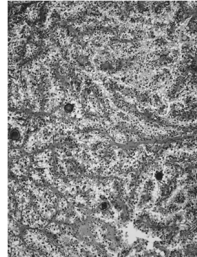
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 - MiTF Family translocation carcinomas (8311/3)
 - Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma (8311/3)

MiTF Family Translocation RCC

- Xp11.2 Translocation – TFE3 Gene
 - Fusion of TFE3 with PRCC, ASPL etc
- *t(6;11)(p21;q12)*
 - *Alpha-TFEB gene fusion*

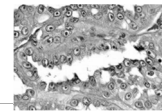
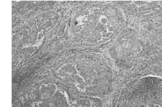
Xp11 Translocation RCC

- 50% of RCC in children and young adults
- Recently described in broad adult age range
- 1-4% adult RCC
- Female predominance: 22:6
- Clinical behavior unclear: possibly aggressive in adults



Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell

- Are rare tumors occurring in the setting of non-renal leiomyomatosis and show germline mutation
- The diagnosis of HLRCC-associated RCC:
 - is made when the characteristic morphological features are identified in the tumor.
 - is confirmed by the presence of germline mutations in *FH* (the gene encoding fumarate hydratase), at 1q42.3-q43.



Grading and Staging

Grading of Renal Tumours

- Many grading systems have been proposed for renal cell neoplasia.
 - The Fuhrman system was the most frequently used grading system in RCC but should not be applied for chromophobe RCC.
 - Furthermore, the Fuhrman system has NOT been validated for most of the new subtypes of renal carcinoma.
 - For these reasons, the four-tiered WHO/ISUP grading system is recommended by the WHO

WHO / ISUP Grading System for CCRCC and Papillary RCC

Grade	Description
Grade 1	Nucleoli are absent or inconspicuous and basophilic at ×400 magnification.
Grade 2	Nucleoli are conspicuous and eosinophilic at ×400 magnification and visible but not prominent at ×100 magnification.
Grade 3	Nucleoli are conspicuous and eosinophilic at ×100 magnification.
Grade 4	There is extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation.

- For grade 1–3 tumors, the system defines tumor grade based on nucleolar prominence.
- Grade 4 is defined by the presence of pronounced nuclear pleomorphism, tumor giant cells, and/or rhabdoid and/or sarcomatoid differentiation.

pT Staging of RCC (AJCC TNM 8 ed. 2017)

- pT1:** Confined to the kidney, ≤ 7 cm
 T1a: ≤ 4 cm
 T1b: > 4 cm, ≤ 7 cm
- pT2:** Confined to the kidney, > 7 cm
 T2a: 7 - 10 cm
 T2b: > 10 cm
- pT3:** Tumor extending a major vein or perinephric fat, but not into the ipsilateral adrenal gland or beyond Gerota's fascia.
 T3a: tumor extending into the renal vein or its segmental branches, or tumor invading the pelvicalyceal system or tumor invading perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota's fascia
 T3b: tumor growing into vena cava below diaphragm.
 T3c: tumor growing into vena cava above the diaphragm or into the wall of the vena cava.
- pT4:** Tumor invading beyond Gerota's fascia including contiguous extension into the ipsilateral adrenal gland

pT Staging of RCC (AJCC TNM 8th Ed. 2017)

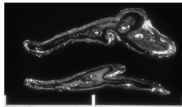
pT3a:

- Word “grossly” was eliminated from the description of renal vein involvement
- “Muscle containing” was changed into “segmental veins”
- Invasion of the pelvicalyceal system was added



Comprehensive Review of Adrenal Gland Pathology

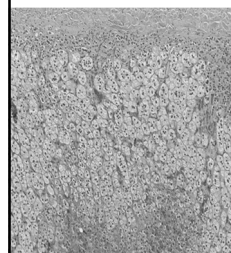
Chin-Lee Wu, M.D., Ph.D.
Director, Urologic Pathology
Massachusetts General Hospital
Associate Professor of Pathology
Harvard Medical School



Normal Adrenal Gland: A Composite of Two Endocrine Organs

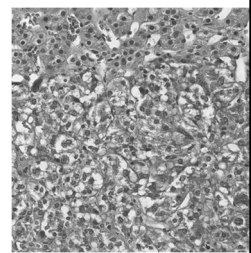
- Cortex: mesoderm derived
- Medulla: neuroectoderm derived
- Normal weight: 6 gm

Normal Adrenal Gland



Cortex

- Zona
- Glomerulosa
 - Aldosterone
 - Fasciculata
 - Glucocorticoid
 - Reticularis
 - Sex hormone



Medulla (catecholamines)

Adrenal Gland: Diagnostic Issues

- Primary Adrenal Tumors vs Metastasis
- Adrenal Cortical Hyperplasia vs Adenoma vs Carcinoma
- Pheochromocytoma
- Neuroblastic Tumors (Neuroblastoma)
- Incidentaloma and FNA

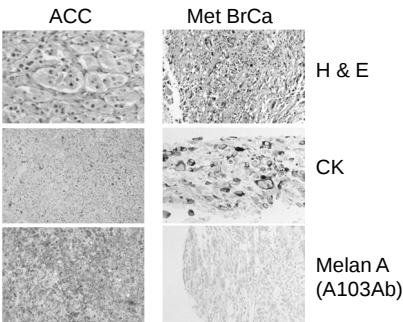
Adrenal Gland Metastasis

- 4th most common site of metastasis (surpassed by lung, liver and bone)
- 27% of 1000 ca. patients at time of autopsy
- 2.5% of adrenal incidentaloma
- Metastatic carcinoma
 - Breast, lung, kidney, GI, ovary,
- Melanoma
- Lymphoma

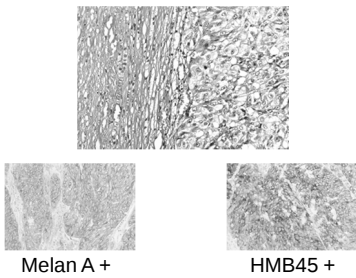
Abrams HL et al Cancer 1950; 3:74-85
Lack EE, 1997. Tumor of the Adrenal Gland and Extra-Adrenal Paraganglia, AFIP
Young 2000, Endocrin. Metabol. Clin. N. America 29:159

Adrenal Cortical Tumor vs Metastatic Ca:
Immunophenotype

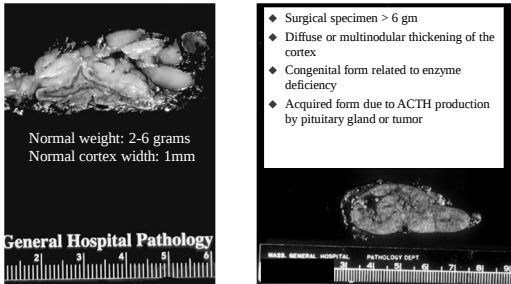
	Epithelial Markers (Cytokeratin)	Melan A (A Melanoma Marker)
Adrenal Cortical Tumor	Weak to Negative	Strongly Positive
Metastatic Carcinoma	Strong Positive	Negative



Metastatic Melanoma

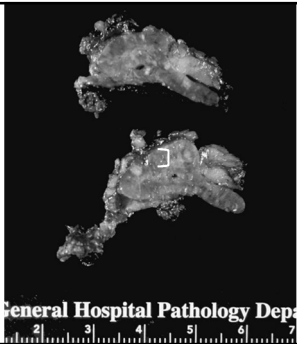


Adrenal Cortical Hyperplasia

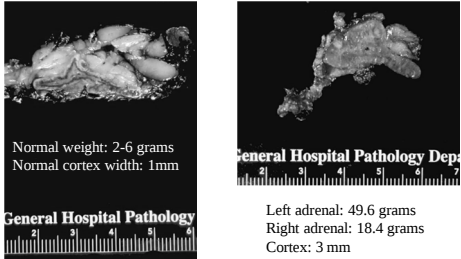


36 yo woman
with bilateral
adrenalectomies

Left adrenal: 49.6 grams
Right adrenal: 18.4 grams
Cortex: 3 mm



Normal vs. Hyperplastic



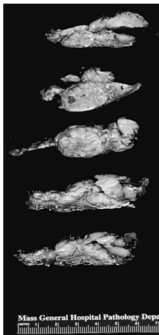
36 yo woman

- What was the underlying cause of the patient's adrenal hyperplasia?
 - Pituitary hypersecretion of ACTH
 - Ectopic non-pituitary secretion of ACTH
 - Iatrogenic ACTH administration

36 yo woman

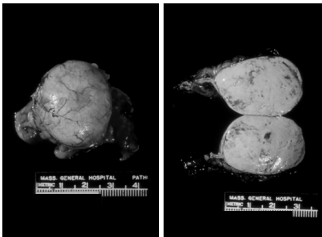
- What was the underlying cause of the patient's adrenal hyperplasia?
 - Pituitary hypersecretion of ACTH
 - Ectopic non-pituitary secretion of ACTH, due to metastatic lung neuroendocrine tumor (carcinoid)
 - Iatrogenic ACTH administration

Adrenal Cortical Adenoma

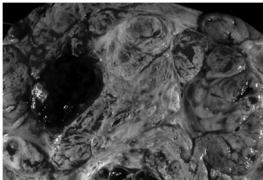


Adrenal Cortical Adenoma

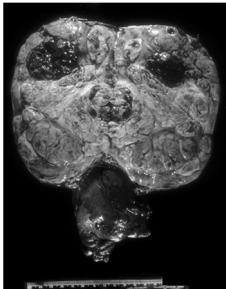
- ◆ Circumscribed, Encapsulated
- ◆ Smooth
- ◆ Bright or Golden Yellow
- ◆ No Necrosis or Hemorrhage



Adrenal Cortical Carcinoma

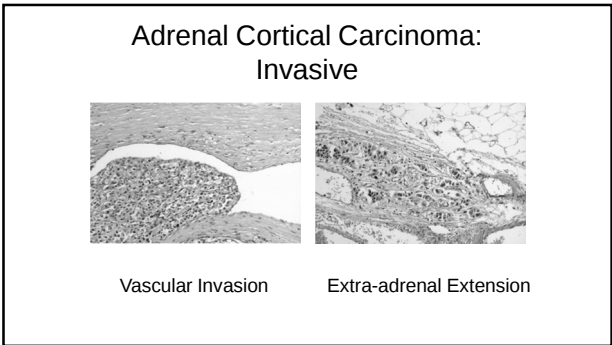
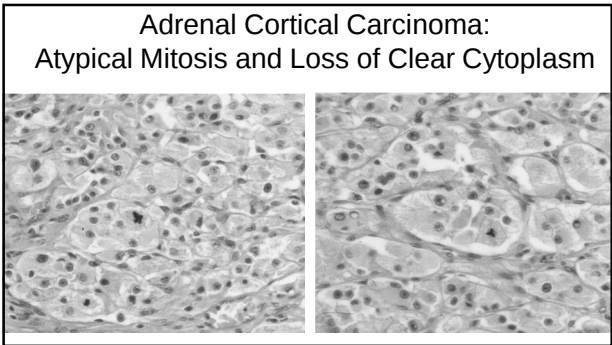
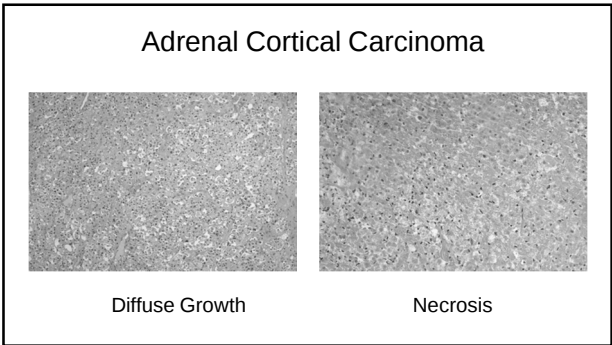
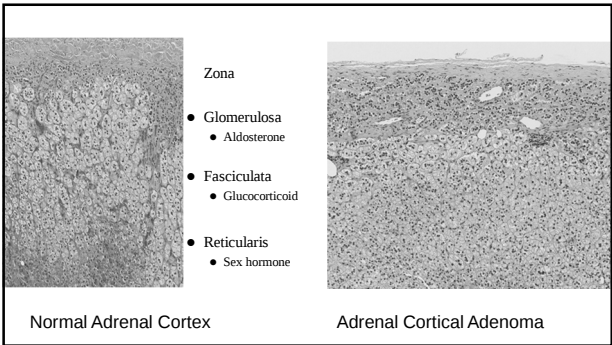


- ◆ Poorly Defined, Invasive
- ◆ Bulky, Coarse, Nodular
- ◆ Yellow, Tan, Brown
- ◆ Necrotic and Hemorrhagic



Adrenocortical Ca vs Adenoma: Weight

Clinically	Benign	Malignant
Tumor < 50 gm	95%	5%
Tumors > 100 gm	5%	95%



Weiss' 9 Histologic Features

1. High Mitotic Rate ($>5/50$ hpf)
2. Atypical Mitosis
3. Venous Invasion
4. High Nuclear Grade (Fuhrman Grade 3-4)
5. Lack of Cells with Clear Cytoplasm ($<25\%$)
6. Diffuse Growth Pattern ($>1/3$ of the Tumor)
7. Necrosis
8. Sinusoidal Invasion
9. Capsular Invasion

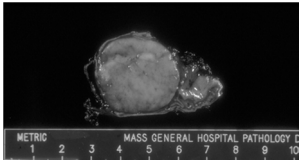
Weiss, Am J Surg Pathol 8:163-169, 1984

Weiss' Histologic Criteria for Adrenal Cortical Tumors

• <u>ADENOMA</u> Presence of 2 or less of the 9 histologic features	• <u>CARCINOMA</u> Presence of 3 or more of the 9 histologic features
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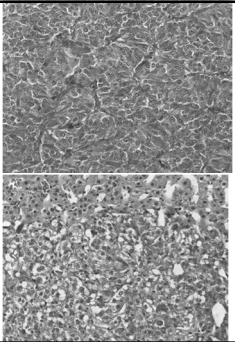
Pheochromocytoma

- Described in 1905 by Poll of the dusk (phoe) color (chromo) tumor exposed to dichromate
- 8/10⁶ person-years in the U.S.
- “ 10% Rule ”
 - Extra adrenal
 - Hereditary / bilateral
 - Pediatric group
 - Malignant potential (2-14%)
 - Non hypertensive
- 2-4 cm, 50-100 gm
- Clinical presentation related to hypersecretion of catecholamine



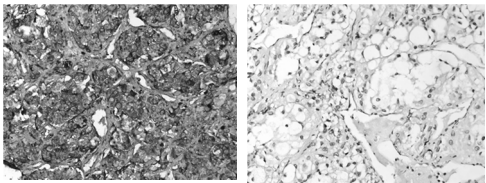
Pheochromocytoma

- Alveolar, trabecular or solid patterns
- Polygonal cells with moderate amount of granular, amphophilic cytoplasm
- Nuclear pseudoinclusion and pleomorphism
- Intra cytoplasmic hyaline granules



Medulla
(catecholamines)

Pheochromocytoma



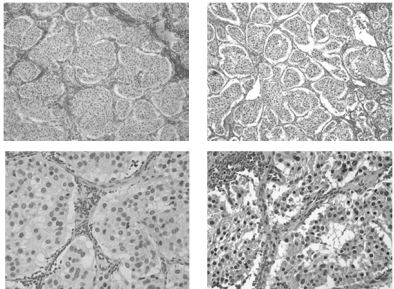
Chromogranin A

S-100 (sustentacular cells)

Pheochromocytoma: Genetic features

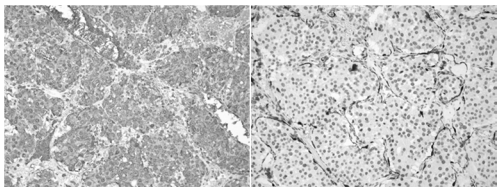
- Familial cases have mutations of proto-oncogene (*RET*) or genes associated with oxygen sensing pathway (*VHL*, *SDHD*, *SDHB*)
 - May result in activation of hypoxic signaling pathways associated with neoplastic transformation
- Germline mutations of *RET*, *VHL*, *SDHD/B* found in ~25% of cases of sporadic pheochromocytoma
 - *VHL* > *SDHD/B* > *RET* (Neumann et al. NEJM 2002)
- Somatic mutations in *RET* and *VHL* found in ~15% of sporadic pheochromocytomas (Eng et al. J Med Genet 1995)

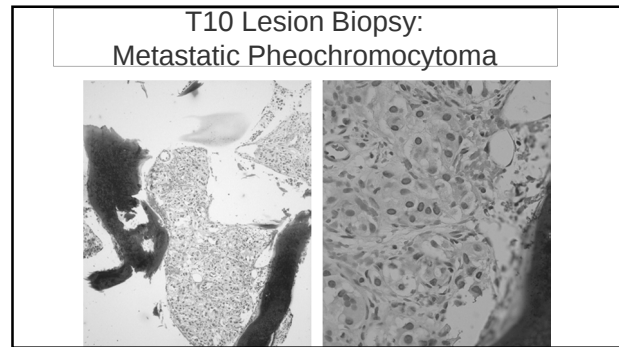
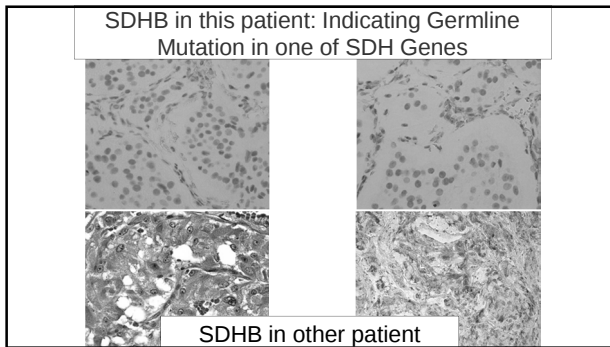
14 yo girl, 10 cm, 330 gm pelvis mass



CgA

S100





Neuroblastoma

- 4th most common tumor in childhood
- 90% 5 years of age or younger
- 90% Adrenal and abdominal sites

Neuroblastoma

- Lobular pattern with fibrovascular septa
- "small blue cell"
- Fibrillar matrix (neuritic cell process)
- Homer Wright pseudorosette
- Immunophenotype:
 - Negative for CK, MIC2
 - Positive for chromogranin A
- Deletion of 1p and amplification of Myc-N gene correlated with poor outcome

Incidence of Adrenal Incidentaloma

- 5.9% in 87,065 autopsies in 25 studies
- Prevalence age dependent:
 - <<1% age 0-19
 - ~0.2% age 20-29
 - ~1.5% age 30-39
 - ~ 7% age > 70
- 1 – 4 % in abdominal CT

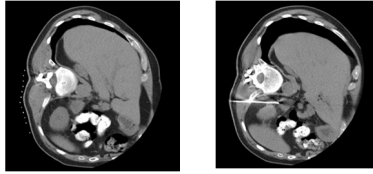
Young 2000, Endocrin. Metabol. Clin. N. America 29:159
Barzon 2000, J Urol. 163:398

Adrenal Incidentaloma

- 11.4% Functioning adenoma
 - 5.3% pre-clinical Cushing's syndrome
 - 5.1% pheochromocytoma
 - 1% aldosterone producing adenoma
- 82.4% non-functioning adenoma
- 4.7% adrenal corticocarcinoma
- 2.5% metastatic cancer

Young 2000, Endocrin. Metabol. Clin. N. America 29:159

Biopsy of Adrenal Incidentaloma



Courtesy of Dr. Mukesh Harisinghani, MGH Radiology

FNA Biology

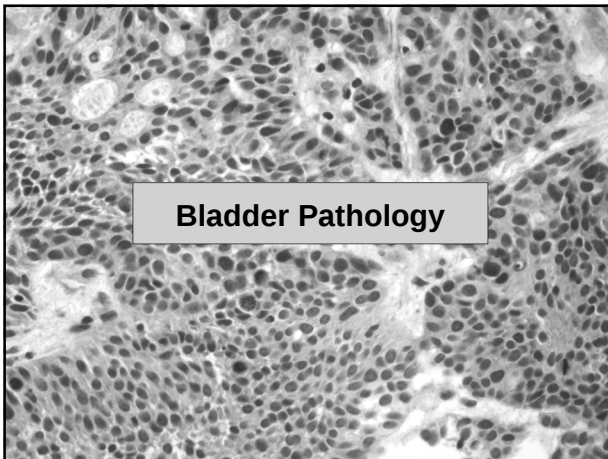
- Primary vs Metastasis
 - Immunological profiles
- Adrenal Cortical Tissue
 - Deciding Normal vs Hyperplasia vs Adenoma can be difficult
 - Adenoma vs Carcinoma may not be definitive.
 - Comments on +/- of Features of ACC
 - ◆ Necrosis
 - ◆ Diffuse/Sheets
 - ◆ Compact/Eosinophilic Cytoplasm
 - ◆ High Mitotic Rate
 - ◆ Pleomorphic/Hyperchromatic
 - ◆ Large Nucleoli
- Adrenal Medullary Tissue
 - Pheochromocytoma

Correlation of Histologic, Radiologic and Clinical Findings

Adrenal Gland: Diagnostic Issues

- Primary Adrenal Tumors vs Metastasis
- Adrenal Cortical Hyperplasia vs Adenoma vs Carcinoma
- Pheochromocytoma
- Neuroblastic Tumors (Neuroblastoma)
- Incidentaloma and FNA

Thank You



Speaker Picture and Bio



- Surgical pathologist at Brigham and Women's Hospital with subspecialty interest in GU and Endocrine Pathology
- Associate Professor of Pathology at Harvard Medical School

Disclosures

- I have no financial interests to disclose

Lecture Outline

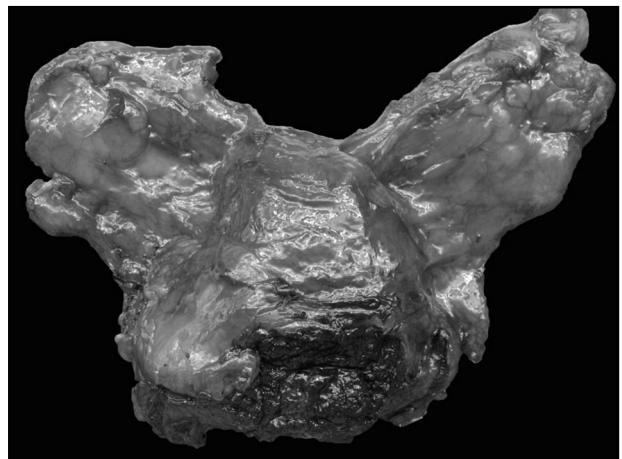
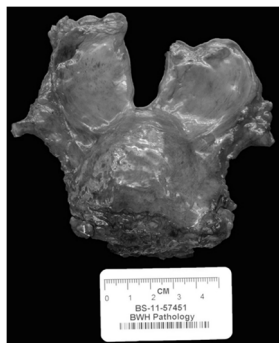
1. Gross evaluation of cystectomy specimens and normal bladder anatomy and histology
2. Introduction to bladder carcinoma: non-muscle invasive versus invasive and papillary versus non-papillary
3. Non-muscle-invasive bladder tumors
 - Papillary tumors
 - Carcinoma in situ
4. Muscle-invasive bladder carcinoma
 - Making the diagnosis
 - Urothelial carcinoma variants
 - Information included in the pathology report for cystectomy specimens
 - Assessment of cystectomy specimens after neoadjuvant therapy
 - Bladder tumors other than urothelial carcinoma

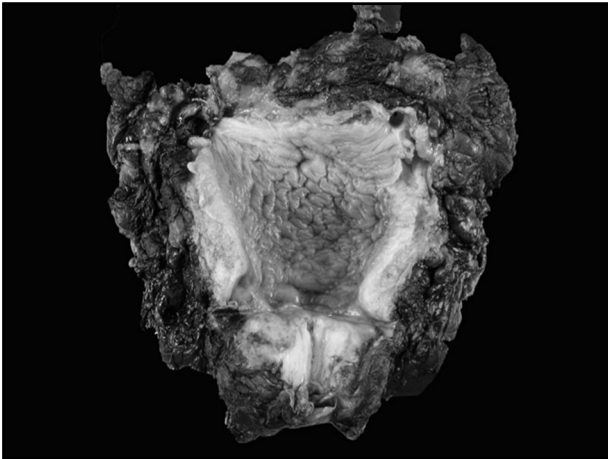
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Gross Evaluation

1. Take gross measurements (bladder, ureters, prostate with seminal vesicles, vagina)
2. Ink the specimen for evaluation of margins and fix it overnight
3. Open the bladder along the anterior wall
4. Describe tumor: location, size, configuration, depth of penetration, gross margin status, etc
6. Submit sections:
 - A. Margins
 - B. Tumor – deepest extent
 - C. Uninvolved bladder, prostate

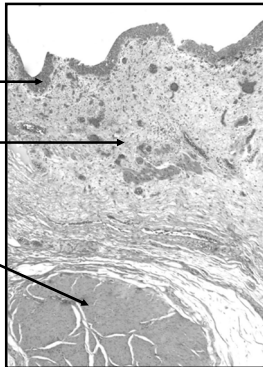




Normal Bladder Anatomy

The bladder is formed of 4 layers:

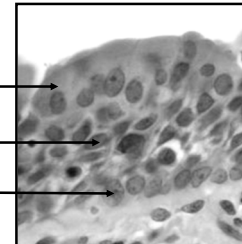
- Urothelium
- Lamina propria (with muscularis mucosae, vascular plexus, +/- adipose tissue)
- Muscularis propria (with adipose tissue intervening)
- Serosa/adventitia with perivesical fat



Normal Urothelium

Normal urothelium is three to seven cell layers, depending on the degree to which the bladder is distended.

- Superficial cells/
umbrella cells
- Intermediate cells
- Basal cells



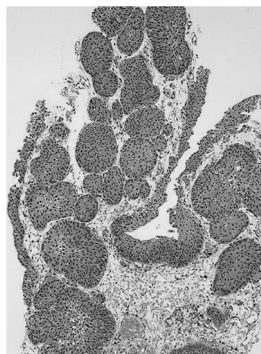
von Brunn's Nests

The most common variant of normal/reactive proliferative change. They represent invaginations of the surface urothelium into the underlying lamina propria.

Pitfalls:

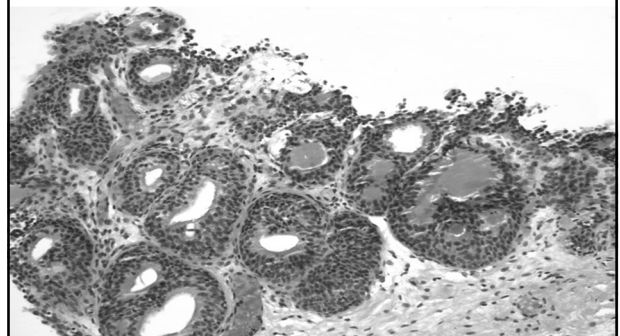
1. Can be hyperplastic mimicking carcinoma.
- Can misinterpret involvement of von Brunn's nests by UCa as invasion.

Have a lobular architecture, with a non-infiltrative base, lack cytologic atypia.



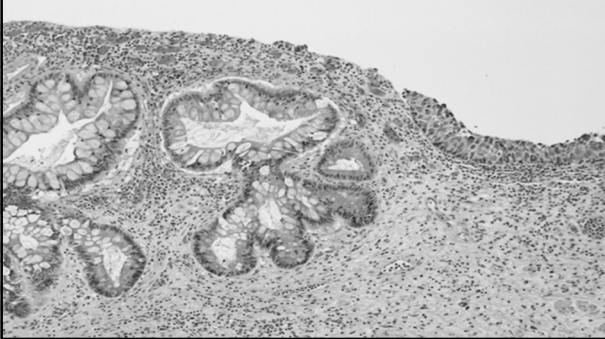
Cystitis Cystica

Part of the spectrum of reactive changes in the bladder, they represent cystically dilated von Brunn's nests.



Cystitis Glandularis

Cystitis cystica with glandular metaplasia, can show intestinal metaplasia.



Lecture Outline

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Bladder Cancer

- 90% of bladder cancers are urothelial carcinoma
- Not all urothelial carcinoma is the same

***Muscle-invasive (MIBC) vs Non-muscle-invasive bladder cancer (NMIBC)

***Papillary vs Non-papillary

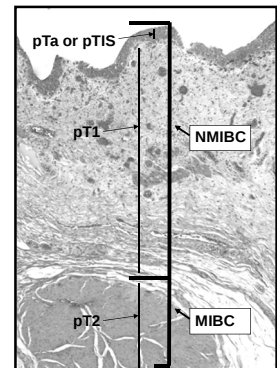
MIBC vs. NMIBC

Bladder cancer can be broken down into superficial/non-muscle invasive (NMIBC) and muscle invasive bladder cancer (MIBC).

NMIBC can be a papillary tumor without extension into the lamina propria (pTa), carcinoma in situ (pTis), or a tumor with invasion into the lamina propria (pT1).

NMIBC accounts for 75% of urothelial carcinomas

70% of NMIBC are pTa, 20% pT1, and 10% carcinoma in situ (CIS).



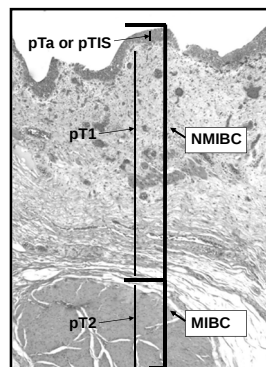
MIBC vs. NMIBC

MIBC arises from:

- CIS
- High-grade non-invasive papillary

Progression from superficial to muscle-invasive disease occurs in only 15% of non-invasive lesions.

Only 15% have had a previous biopsy showing NMIBC, the remaining 85% are diagnosed as muscle invasive on first biopsy.

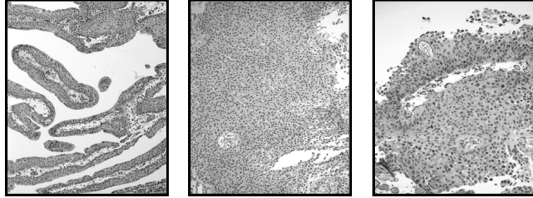


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Papillary Urothelial Tumors

Range from benign and malignant with a spectrum of changes in: thickness of urothelium, polarity, cytologic atypia, nuclear pleomorphism, mitotic activity, apoptotic cells.



Papillary Urothelial Tumors

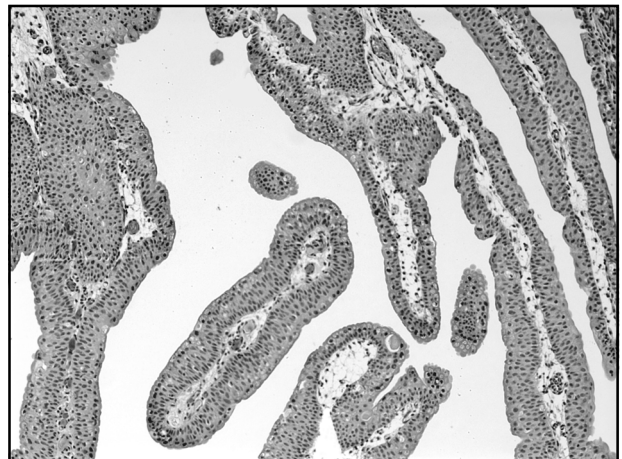
- Papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Papillary Urothelial Carcinoma, Low Grade
- Papillary Urothelial Carcinoma, High Grade

Papillomas

Clinical History: Rare, 1-2% of papillary tumors, occur in younger patients (should be confined to patients <50 years)

Histology:

- Small, solitary
- Delicate finger-like non-branching papillae lined by
- Urothelium of normal thickness (3-7 cell layers)
- With normal polarization and maturation (intact superficial umbrella cells)
- Minimal cytologic atypia: atypia confined to the umbrella cells
- No mitotic figures



Papillary urothelial neoplasia of low malignant potential (PUNLMP)

The histology is virtually the same as a papilloma though it can have slightly thicker urothelium lining the papillae.

If a tumor looks like a papilloma but the patient is over 50, best to diagnose it as PUNLMP.

Grading of Papillary Urothelial Carcinoma

Grading scheme important in NMIBC – once you have muscle invasion they are virtually all high grade carcinomas

Purpose of this grading system is to predict recurrence and progression.

Based on features including: polarity, cytologic atypia, nuclear pleomorphism, mitotic activity, and apoptotic cells.

Factors Influencing Recurrence and Progression

Table 5 - Weights used to calculate the recurrence and progression scores

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
>8	6	3
Tumor size		
<3 cm	0	0
>3 cm	3	3
Prior recurrence rate		
Primary	0	0
<1 rec/yr	2	2
>1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	8
Grade		
G1	0	0
G2	1	0
G3	2	1
Total score	0-17	0-23

Sylvester et al. European Urology, 2009.

Disease Progression in pTa Tumors

pTa tumors frequently recur (recurrence seen in 50-70%), progression also occurs.

WHO/ISUP Classification	Progression Risk (%)	T1 (%)	T2/T2+(%)
LOW	~11.5	~10	~1.5
HIGH	~45	~31	~14

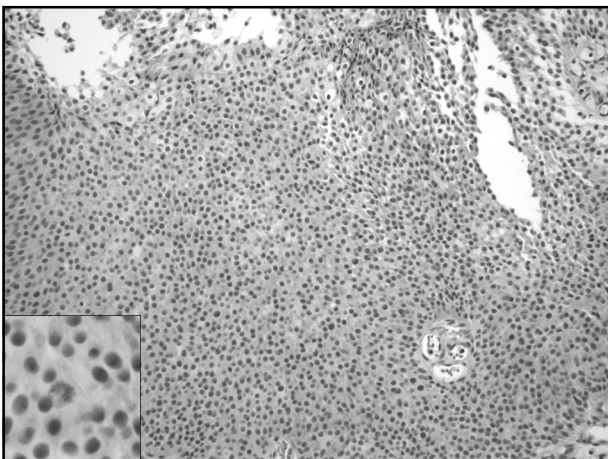
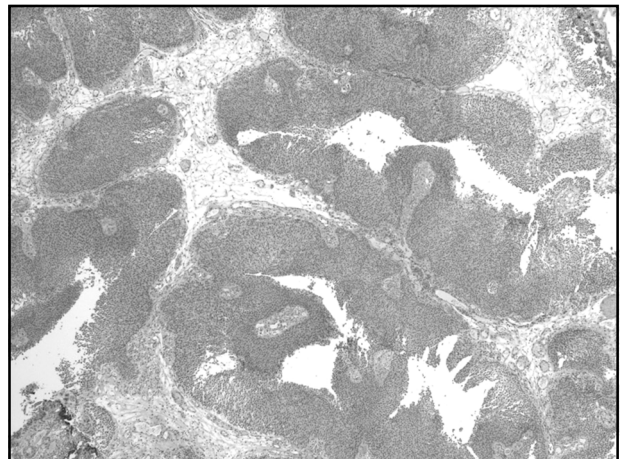
*progression defined as recurrence with invasion into lamina propria or beyond, follow-up period of 7.5 years

Samaratunga et al. Urology. 60:315-319, 2002.

Papillary Urothelial Carcinoma, Low Grade

Histology:

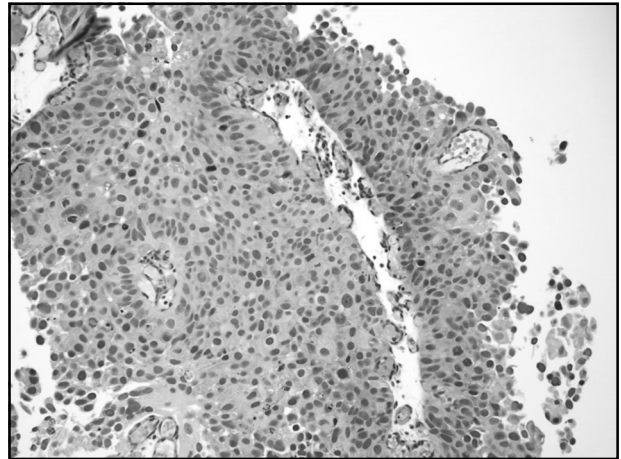
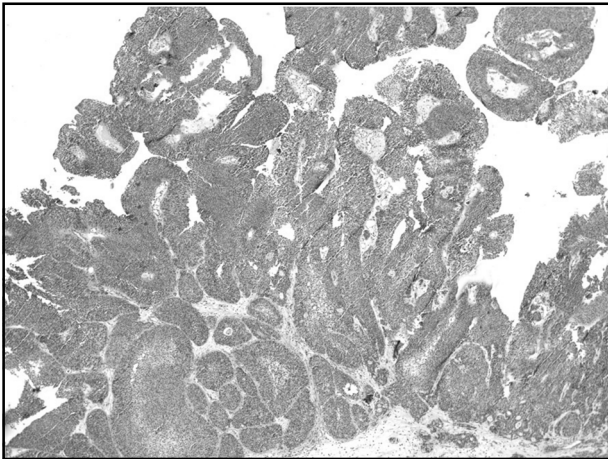
- Branching papillae
- Lined by urothelium >7 cell layers
- Intact polarization
- Uniform cells (may have grooved nuclei)
- Mild cytologic atypia (but more than PUNLMP),
- Low mitotic activity (limited to lower half of the urothelium)



Papillary Urothelial Carcinoma, High Grade

Histology:

- Branching papillae
- Lined by urothelium >7 cell layers
- Lack of polarity, disorganized architecture, discohesive
- Cellular pleomorphism moderate to marked
- Nuclear enlargement and hyperchromasia
- Frequent mitoses (throughout the layers of urothelium)

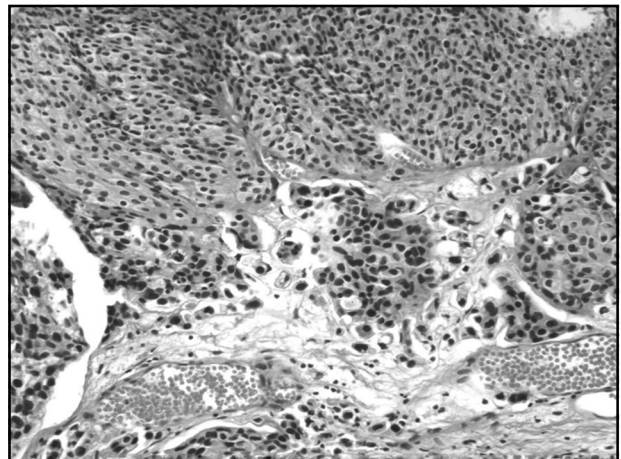


Lamina Propria Invasion

For NMIBC 70% are pTa, 20% pT1, and 10% carcinoma in situ (CIS).

What we see histologically: single cells, nests of cells with irregular borders, paradoxical differentiation (cells have more cytoplasm and the cytoplasm is more eosinophilic), desmoplasia, retraction artifact. Invasion into lamina propria can be the core of the papillae or at the base.

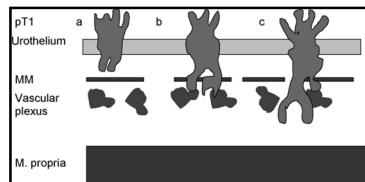
Pitfalls: tangential sectioning, obscuring inflammation, cautery artefact (significant issue resulting in interobserver variability).



Extent of Lamina Propria Invasion

Currently we do not substage T1 tumors.

AJCC recommends including a comment regarding extent of lamina propria invasion, though how to characterize extent is not established.



Rhijn et al. Europ. Urol. 56:430-442, 2009.

Some studies have used invasion or muscularis mucosae.

Other studies have used depth of invasion or millimeters of invasive tumor in lamina propria.

Lecture Outline

1. Gross evaluation of cystectomy specimens and normal bladder anatomy and histology
2. Introduction to bladder carcinoma: non-muscle invasive versus invasive and papillary versus non-papillary
3. Non-muscle-invasive bladder tumors
 - Papillary tumors
 - Carcinoma in situ
4. Muscle-invasive bladder carcinoma
 - Making the diagnosis
 - Urothelial carcinoma variants
 - Information included in the pathology report for cystectomy specimens
 - Assessment of cystectomy specimens after neoadjuvant therapy
 - Bladder tumors other than urothelial carcinoma

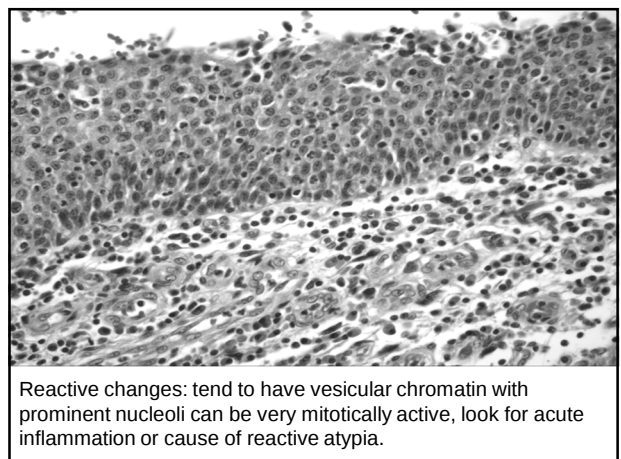
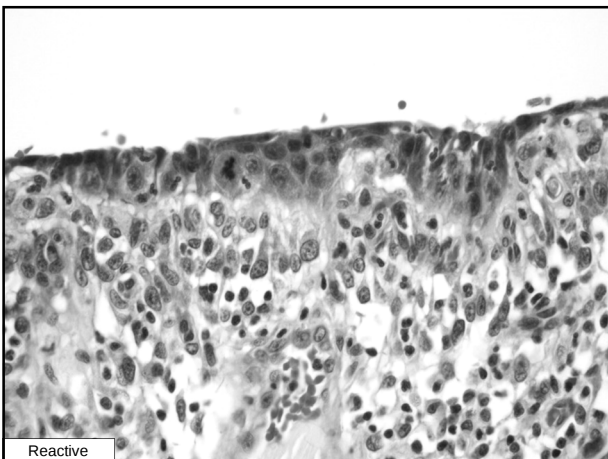
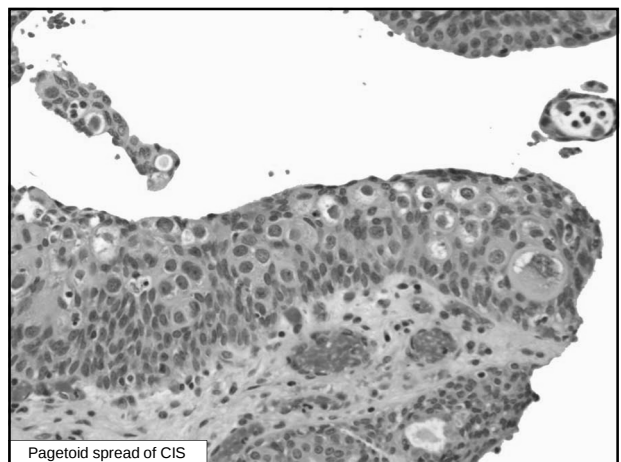
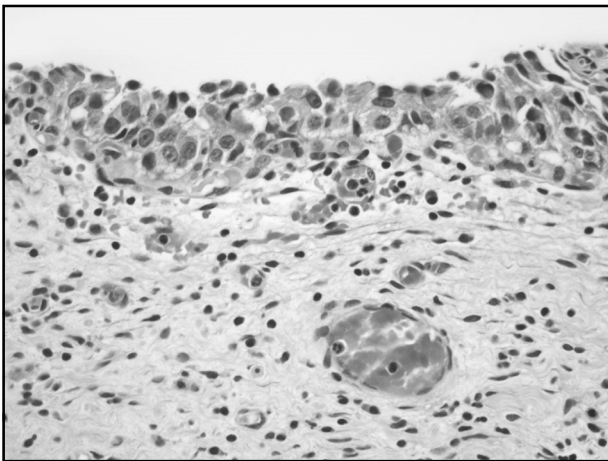
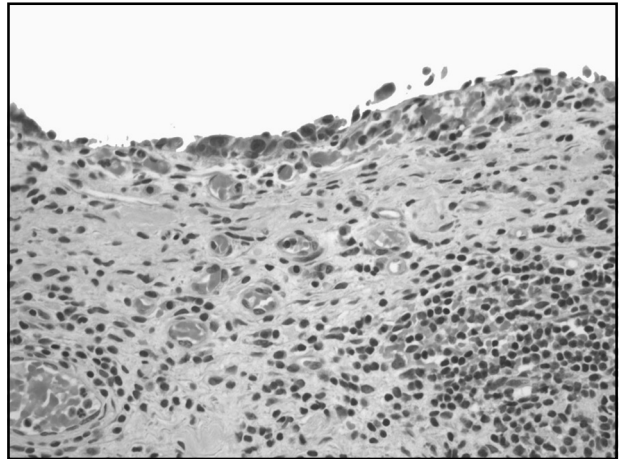
Carcinoma In Situ (CIS)

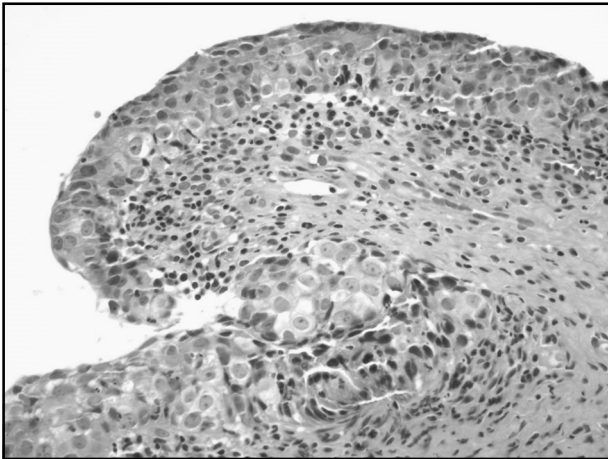
Urothelial Dysplasia:

- In dysplasia the thickness is normal (<7 cells layers).
- High grade dysplasia = CIS

Histologic Features:

- Requires UNEQUIVOCAL severe cytologic atypia
- Enlarged hyperchromatic nuclei
- High N:C ratio (though cells retain quite a bit of cytoplasm).
- Clinging CIS: cells are dyscohesive so get sloughing
- CIS can be up to 7 cell layers thick
- Mitotic active
- Hypervascularity in the lamina propria (correlates with red areas on cystoscopy)





Immunohistochemistry for CIS

A panel with p53, CK20, and CD44 may aid in the diagnosis of CIS:

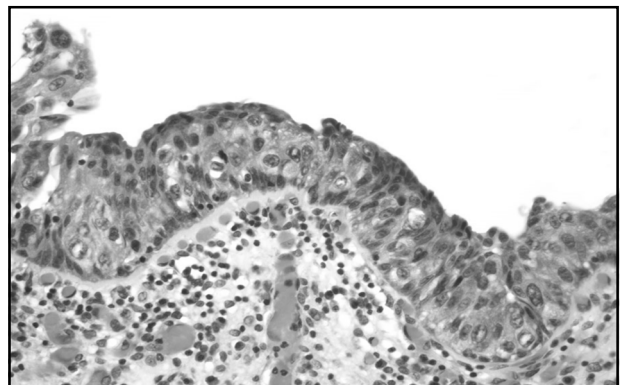
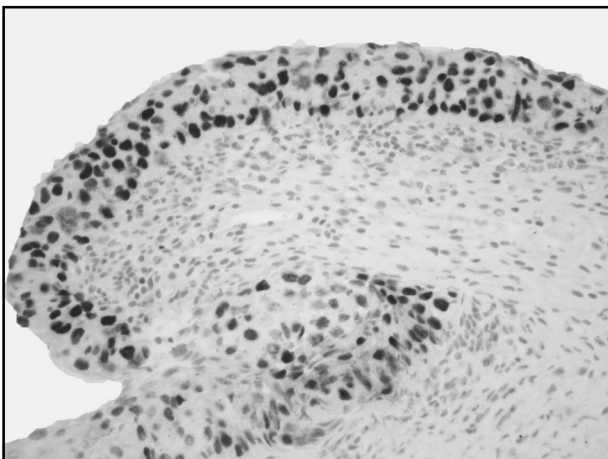
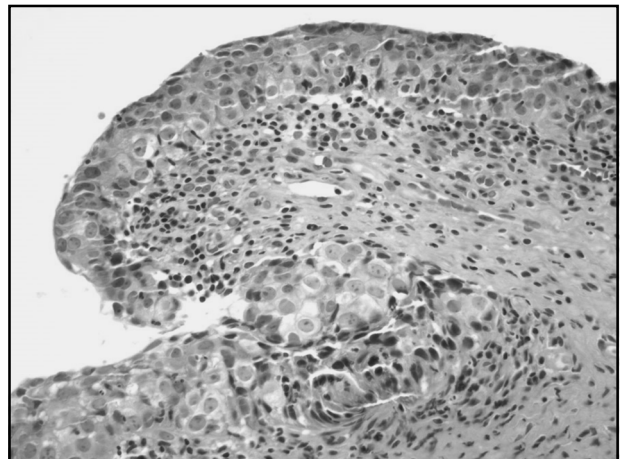
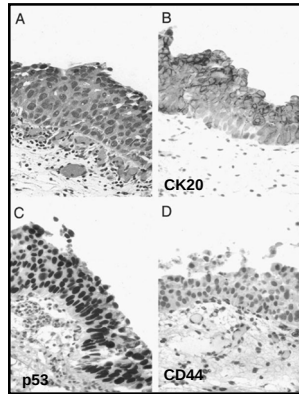
- p53 is a tumor suppressor protein. In normal urothelium p53 is negative or shows scattered weakly positive cells.
- CK20 belongs to the epithelial subgroup of cytokeratin-associated intermediate filaments. In normal urothelium, CK20 expression is confined to scattered umbrella cells
- CD44 is a transmembrane glycoprotein involved in cell-surface binding to collagen. In normal urothelium, CD44 is expressed in the basal cells.

Impox for CIS

Study of 21 cases of CIS:

- 57% showed p53 positivity in the majority (>50%) of malignant cells.
- 81% of CIS showed intense CK20
- 56% showed reduced CD44 staining in the basal cells

McKenney et al. Am J Surg Pathol. 25(8):1074-1078, August 2001.



Shoulders of high grade papillary lesions can look like CIS.

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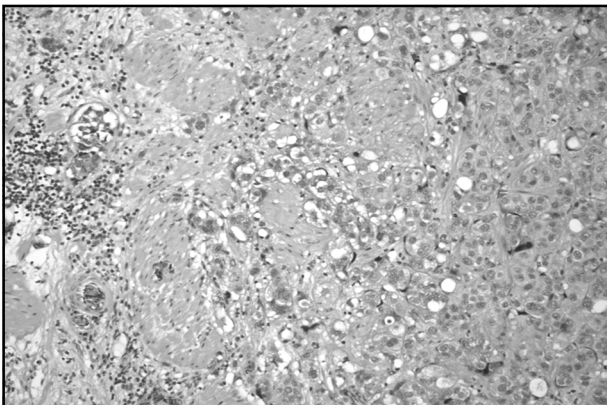
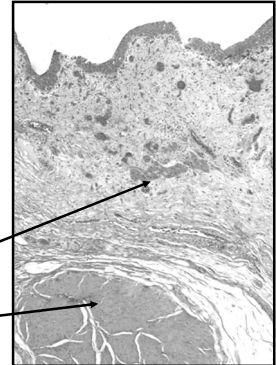
MIBC

Unequivocal invasion into muscularis propria is required since the diagnosis of invasion into muscularis propria prompts cystectomy (with or without neoadjuvant chemotherapy).

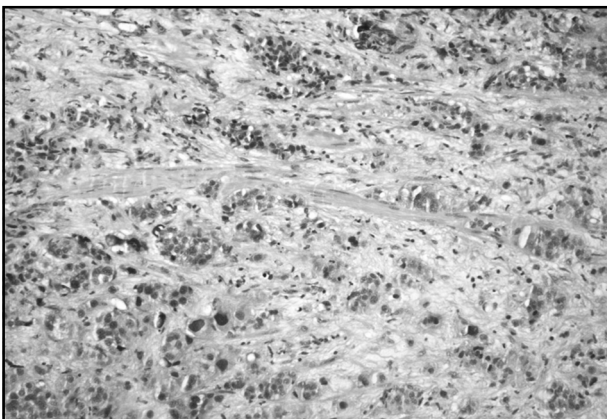
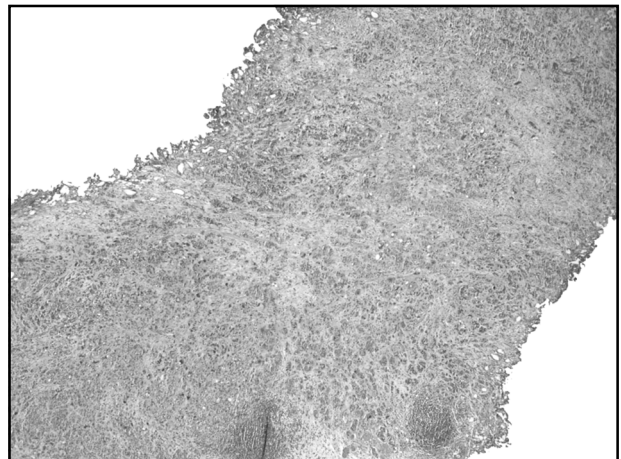
Muscle bundles of muscularis propria are much thicker than those of muscularis mucosae.

Muscularis mucosae

Muscularis propria



Tumor invading muscularis propria: must see unequivocal invasion of thick muscle bundles.



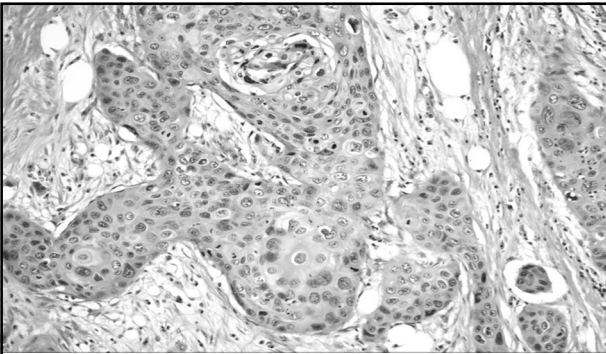
Tumor invading muscularis mucosae: tumor is invading thin strands of muscle

Urothelial Carcinoma Variants

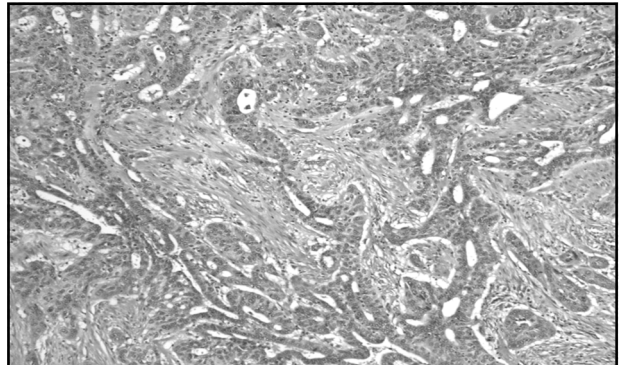
Urothelial carcinoma can have variant morphology.

Variants Include:

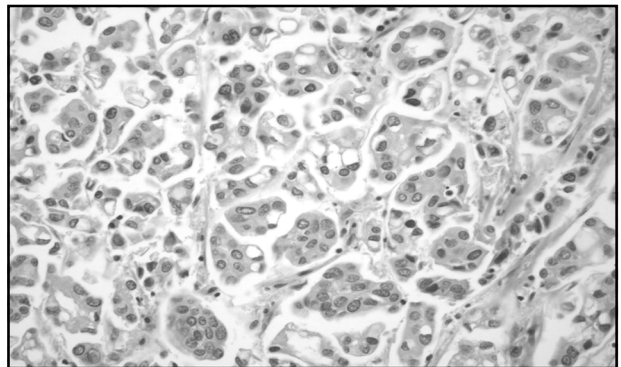
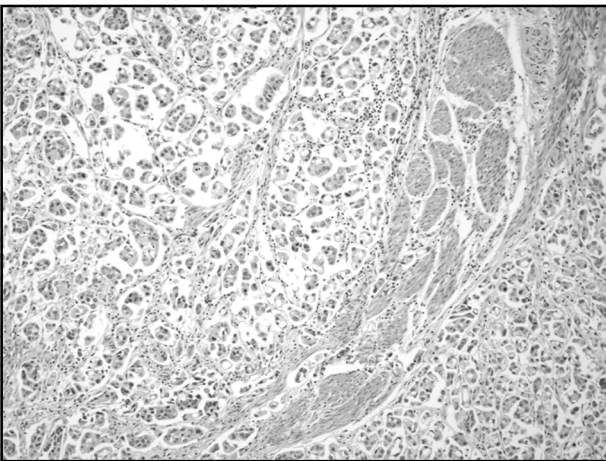
- Squamous differentiation
- Glandular differentiation
- Micropapillary differentiation
- Nested
- Sarcomatoid differentiation



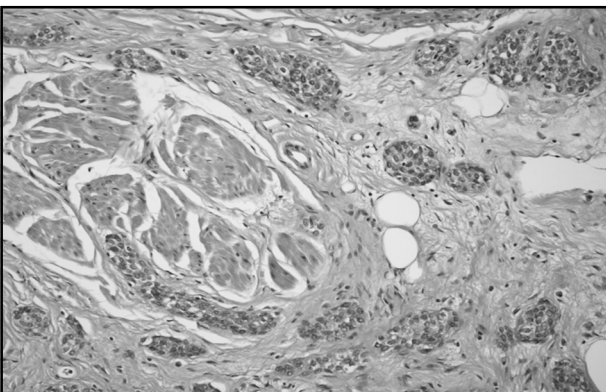
Squamous differentiation: seen in 20-50% of cases. Some data suggesting that it may predict a more limited response to neoadjuvant chemotherapy.



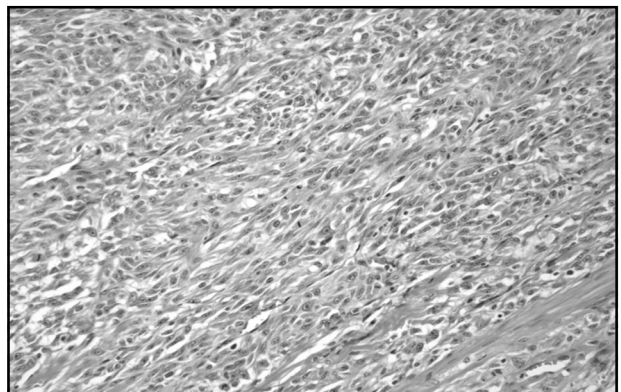
Glandular differentiation: seen in ~10% of cases. Prognostic significance and its implication for response to neoadjuvant chemotherapy is not established.



Micropapillary differentiation: seen in ~2% of cases. Associated with advanced stage and poor prognosis.



Nested variant: deceptively bland, aggressive behavior. Tend to present as high-stage tumors.



Sarcomatoid differentiation: aggressive behavior, poor response to neoadjuvant therapy

Information in Pathology Reports for Cystectomy Specimen

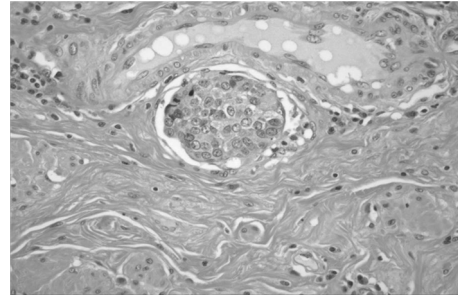
What we include: Tumor type, tumor size, extent of invasion, lymphovascular invasion, margin status, lymph node status, stage

AJCC Stage: the most important determinant of prognosis.

Ta	Papillary tumor without invasion into lamina propria
Tis	Carcinoma in situ
T1	Invasion into lamina propria
T2a	Invasion into superficial (inner half) of muscularis propria
T2b	Invasion into deep (outer half) of muscularis propria
T3a	Tumor microscopically invades perivesical tissue
T3b	Tumor macroscopically invades perivesical tissue
T4a	Tumor invades prostatic stroma, uterus, or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N1	Metastasis to single lymph node in true pelvis
N2	Metastasis to multiple lymph nodes in true pelvis
N3	Lymph node metastasis to common iliac nodes

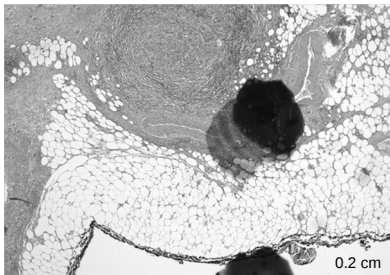
Lymphovascular Invasion

LVI (seen in up to 40% of cases) has been shown to be prognostically significant. Kassouf et al. Eur Urol 2006.



Margin Status

Up to 4% of cases have positive margins. The 5-year cancer specific survival rates of 32 and 72% were found for patients with and without positive surgical margins, respectively. Dotan et al. J Urol 2007.

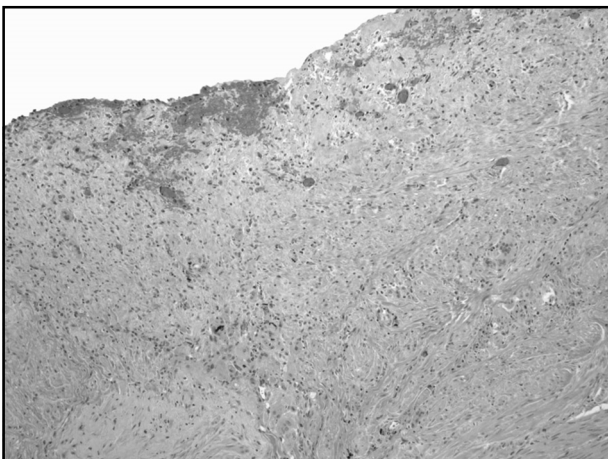


Neoadjuvant Cases

As compared with radical cystectomy alone, the use of neoadjuvant chemotherapy (M-VAC*) followed by radical cystectomy is associated with improved survival in patients with locally advanced bladder cancer (pT2-pT4).

~40% of patients have a complete pathologic response (ypT0). Patients with a complete response do significantly better than those with residual disease (85% are alive at 5 years). Grossman et al. NEJM. 349: 859-866, August 2003.

*M-VAC: methotrexate, vinblastine, doxorubicin (adriamycin), and cisplatin



Other Bladder Tumors

Urothelial carcinoma accounts for 90% of bladder tumors; however, other tumors do occur.

-Squamous cell carcinoma

Only call it squamous cell carcinoma if there is no conventional urothelial carcinoma present; rare tumor, higher incidence in areas with schistosomiasis.

- Adenocarcinoma

- Small Cell Carcinoma

- Clear Cell Adenocarcinoma

- Metastatic Tumors

- Sarcomas: such as rhabdomyosarcoma

Adenocarcinoma

By definition the tumor is comprised entirely of glandular elements. Primary pure adenocarcinomas are rare (2.5% of bladder malignancies).

Split into urachal carcinoma and non-urachal. Non-urachal adenocarcinomas are associated with a worse prognosis.

Different histologic types: NOS (non-descript glands), enteric (colonic) type, mucinous (colloid), clear cell.

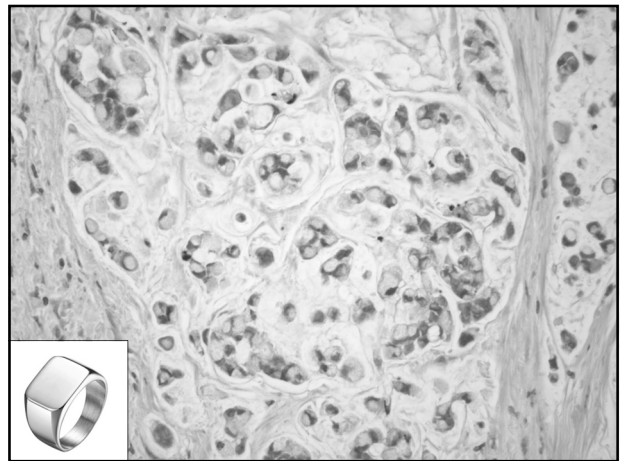
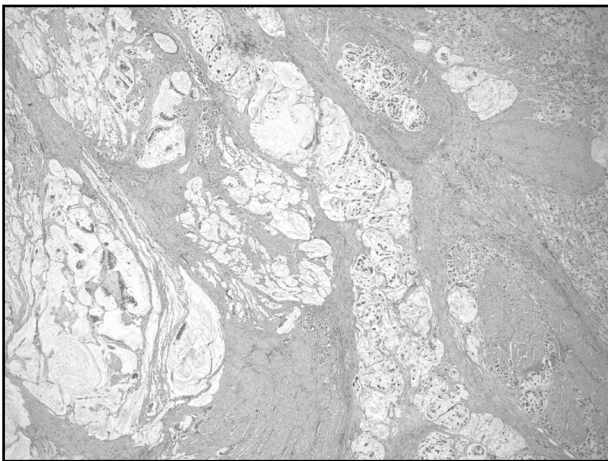
Must consider metastases in the differential diagnosis.

Urachal carcinoma

Defined as primary carcinoma derived from urachal remnants.

For a tumor to be considered urachal it should be localized to an area near or at the dome, the overlying bladder epithelium may be ulcerated but no in situ carcinoma, and glandular metaplasia is absent.

Most often they are mucinous (colloid), but can also be enteric, signet ring cell or mixed.



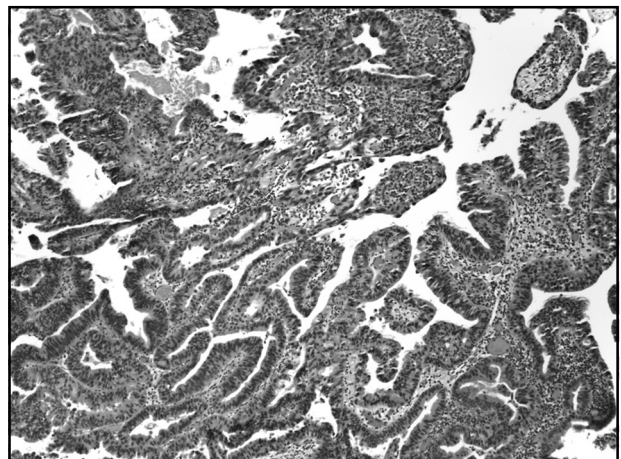
Primary vs Metastasis

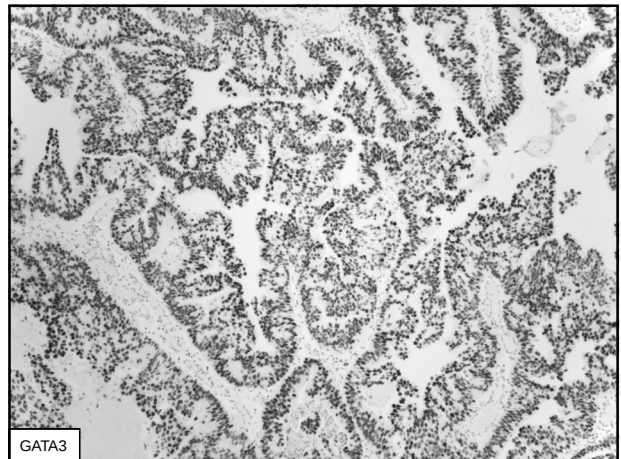
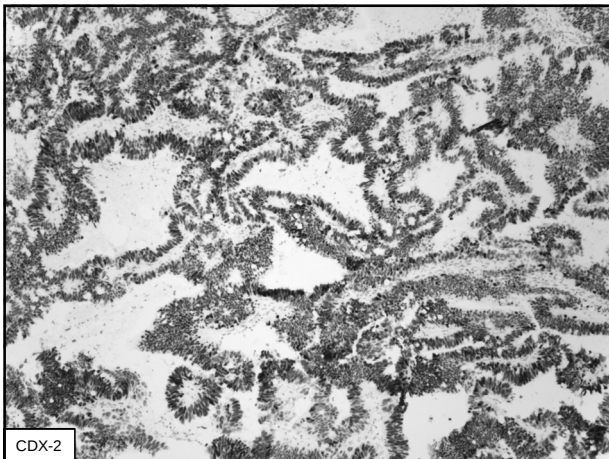
Often immunohistochemistry is not too helpful. Typical urothelial carcinomas are CK7 positive (90%), CK20 positive (65%), p63 positive (85%), 34BE12 positive (65%), GATA3 (75%).

Adenocarcinomas of the bladder often lose p63 and 34BE12 expression and CK7 may be reduced.

GATA3 positive in up to half of cases.

CDX-2 (positive in gastrointestinal tumors) can be positive (and can be diffuse and strong).



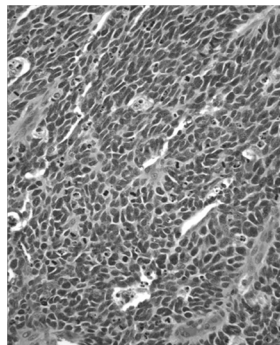


Small Cell Carcinoma

Characterized by an aggressive clinical course. Important to make the diagnosis since it will influence chemotherapy.

Histologically characterized by cells with high N:C ratio, with nuclear molding, numerous mitoses, and apoptotic cells.

Can use stains such as synaptophysin and chromogranin – markers of neuroendocrine differentiation to confirm histologic impression.



Testicular Tumors

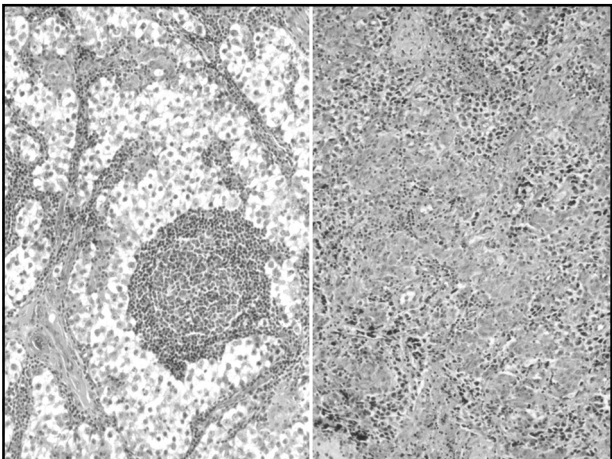
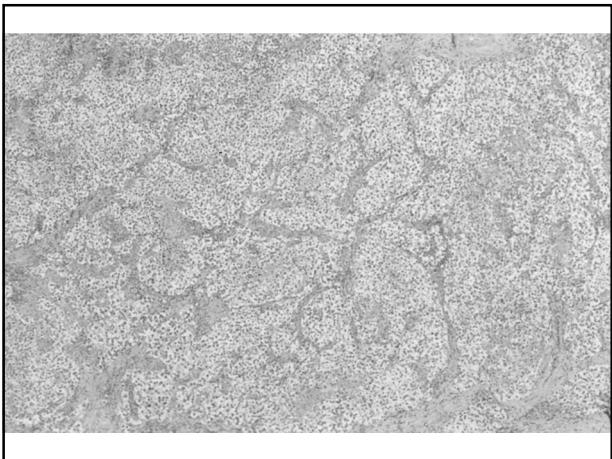
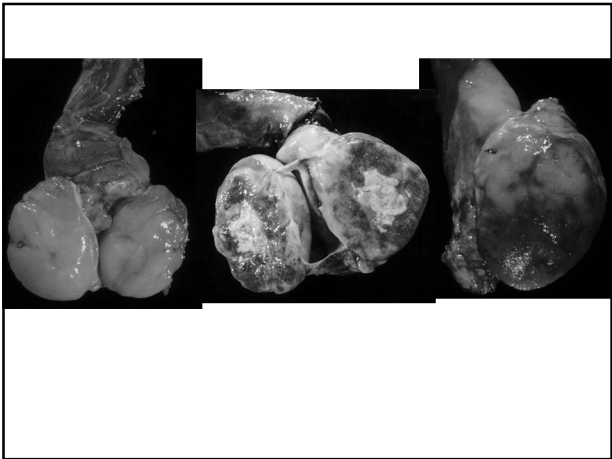
Dr R.H. Young

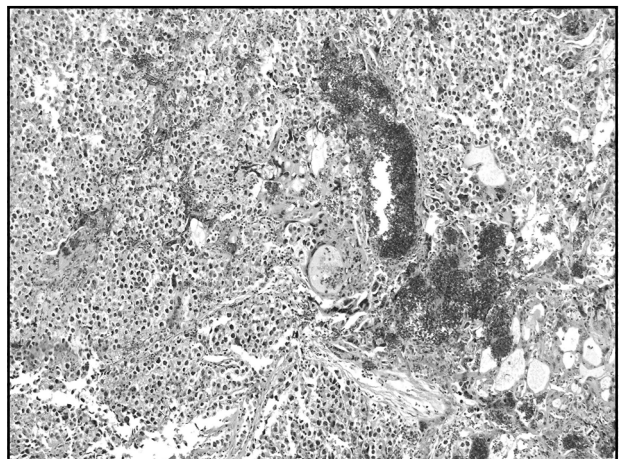
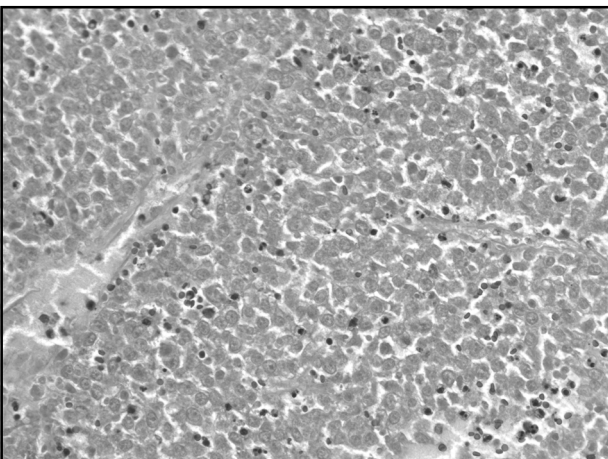
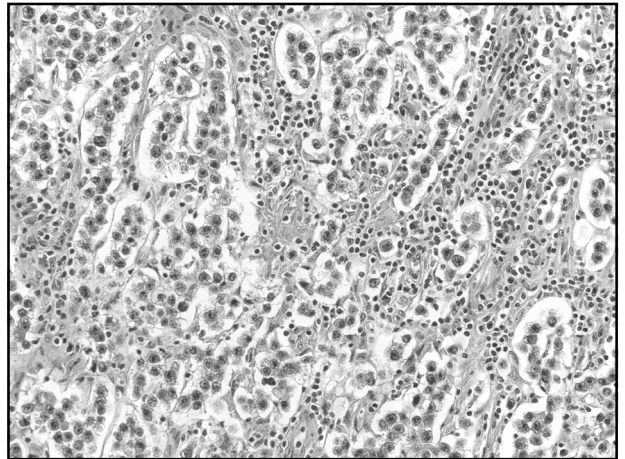
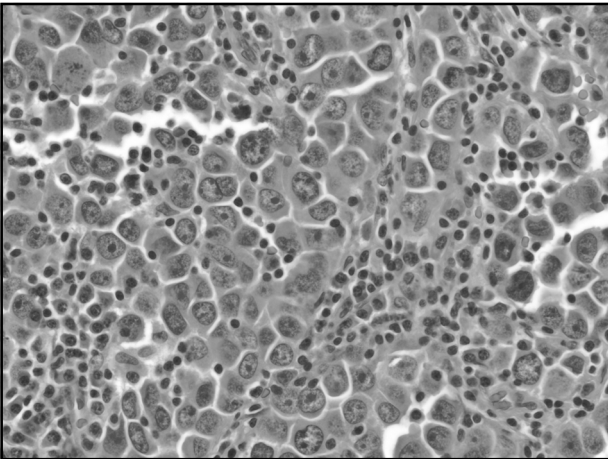
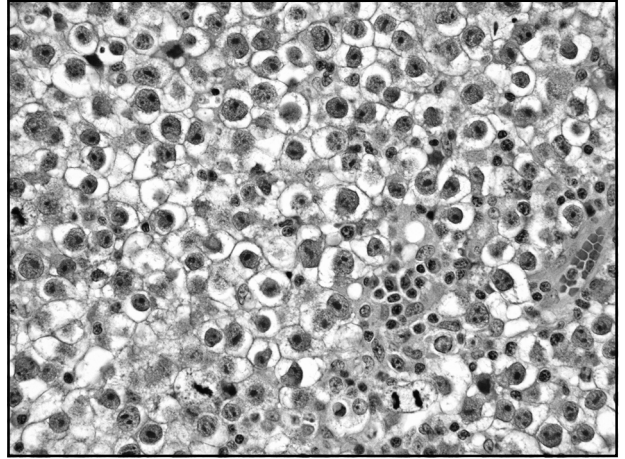
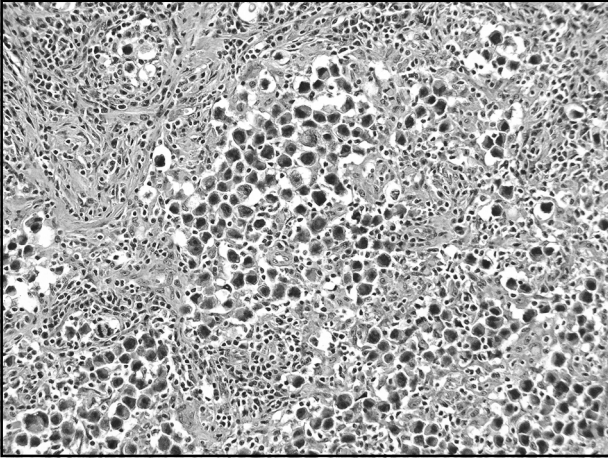
Disclosure Statement

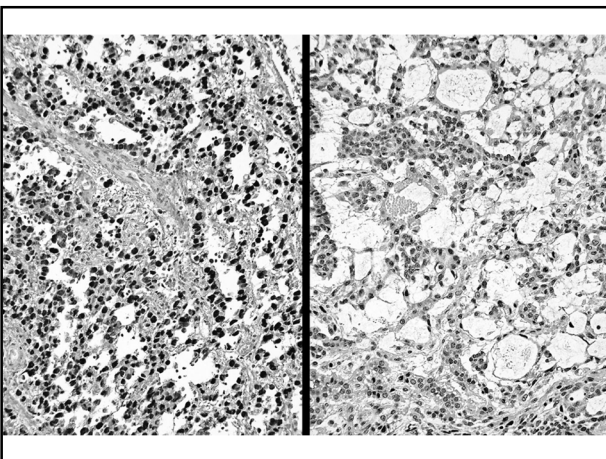
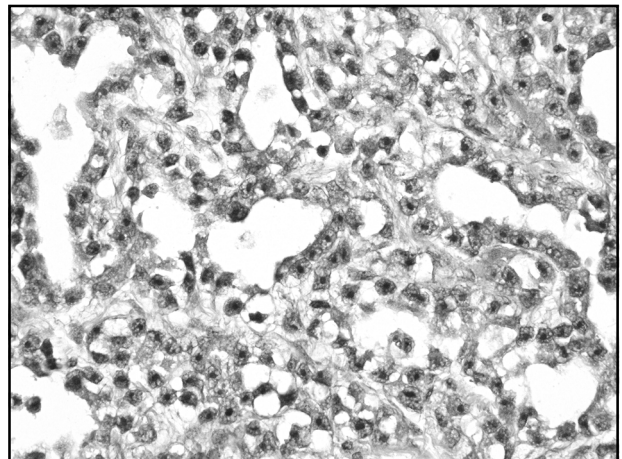
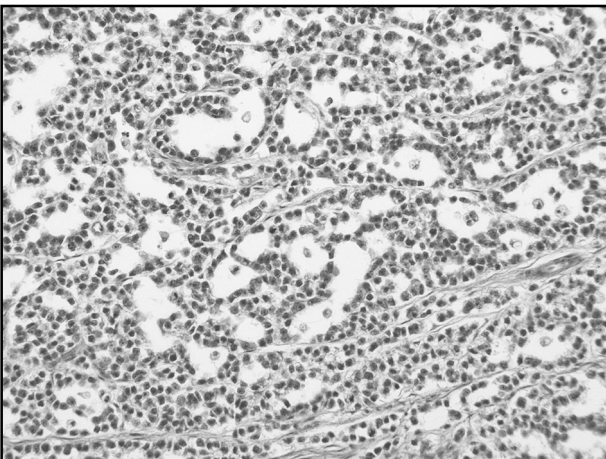
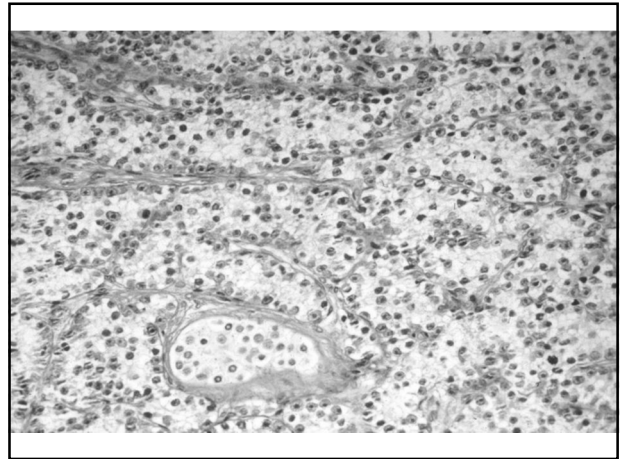
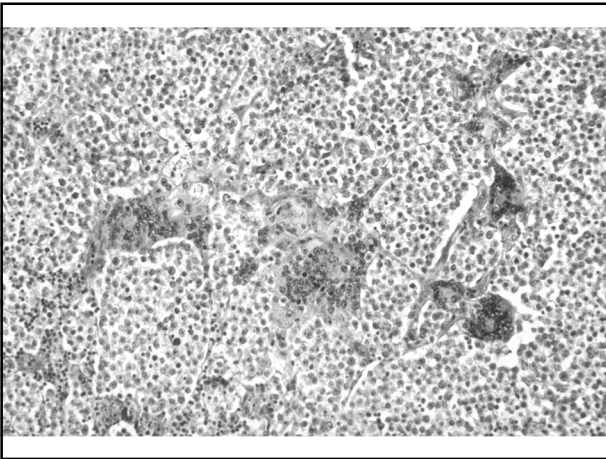
- Nothing to disclose

Germ Cell Tumors

Pure	67%	
Seminoma	53%	
Typical		52%
Spermatocytic		1%
Embryonal ca		10%
Teratoma	3%	
Yolk sac tumor	0.4%	
Polyembryoma	0.3%	
Choriocarcinoma	0.3%	
Mixed	33%	





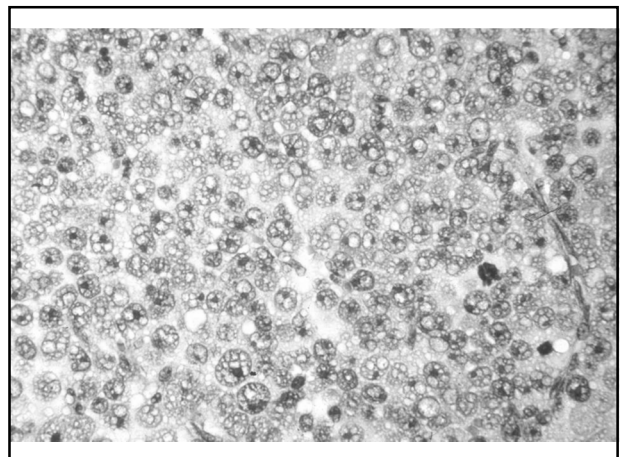
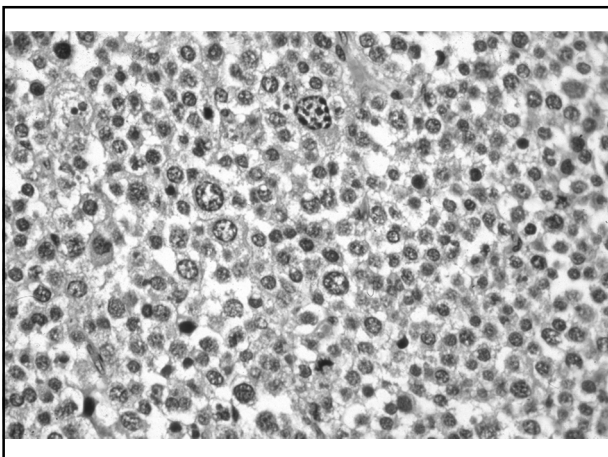
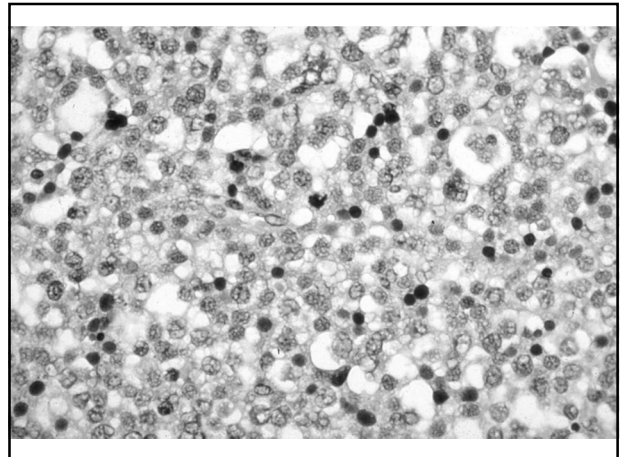
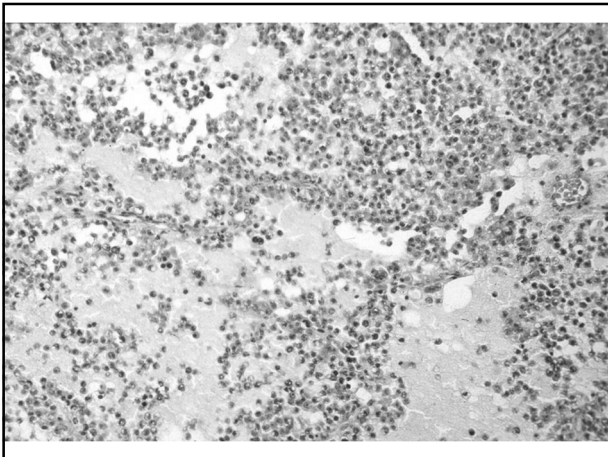
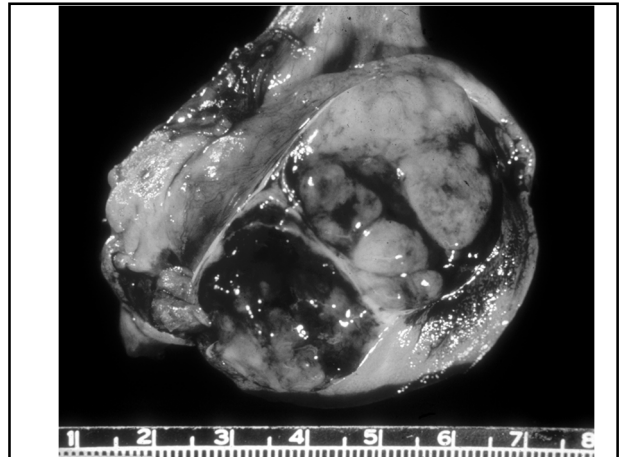


SEMINOMA – DIFFERENTIAL DIAGNOSIS

1. **Spermatocytic seminoma**
2. **Embryonal carcinoma**
3. **Choriocarcinoma**
4. **Solid yolk sac tumor**
5. **Lymphoma**
6. **Sertoli cell tumor**

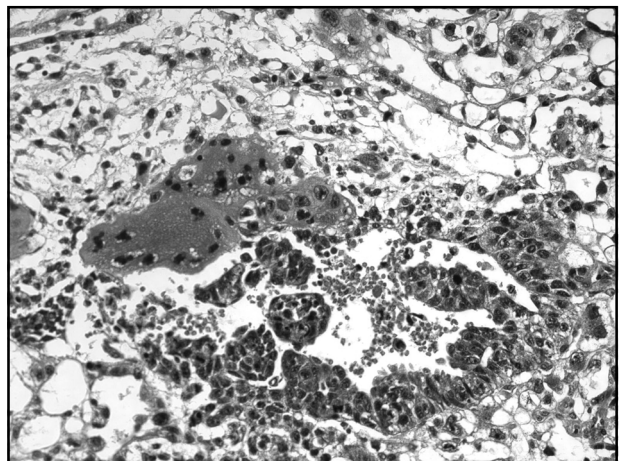
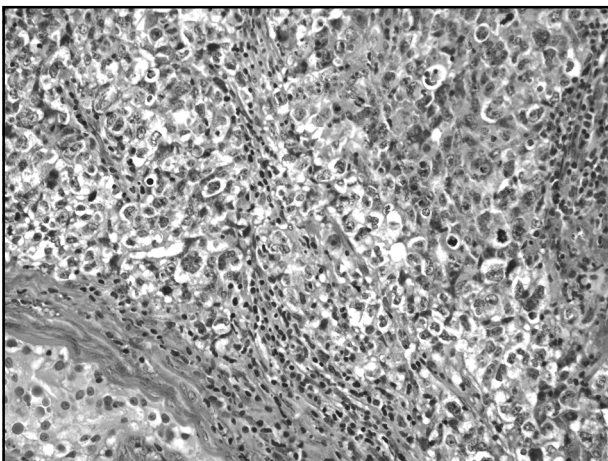
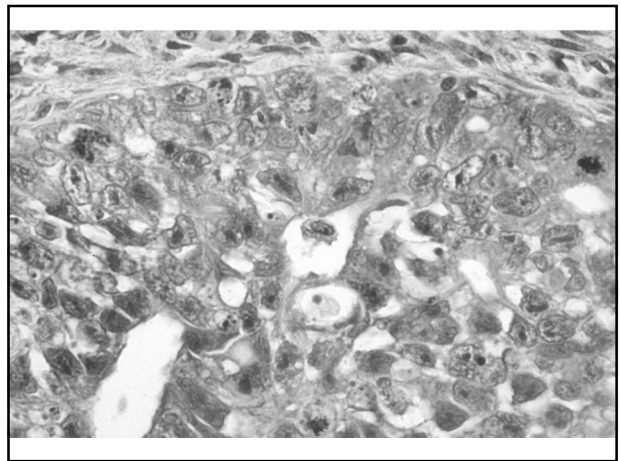
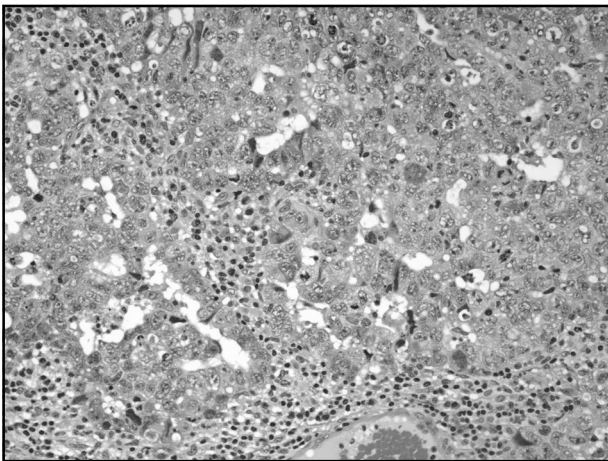
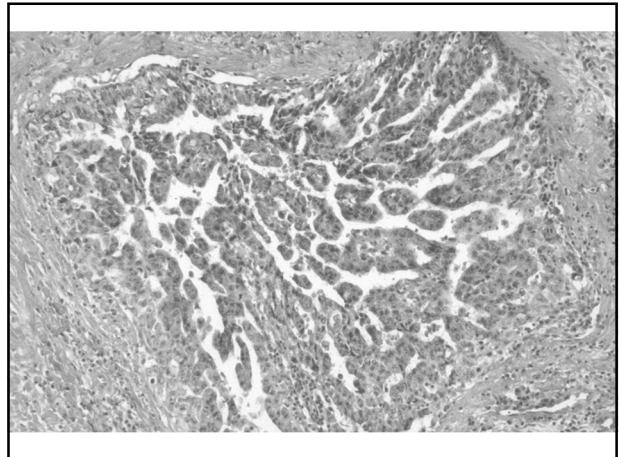
**SPERMATOCYTIC
SEMINOMA**

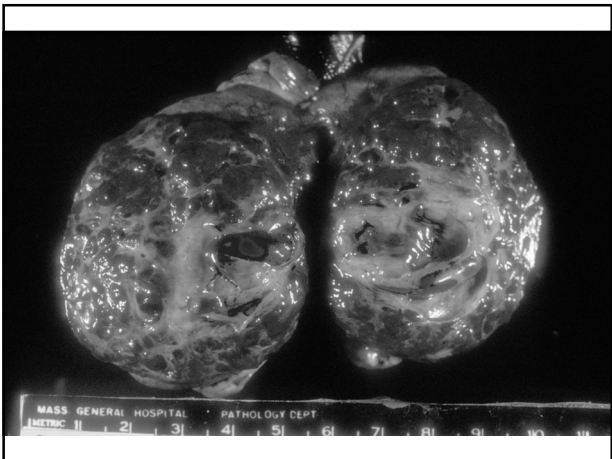
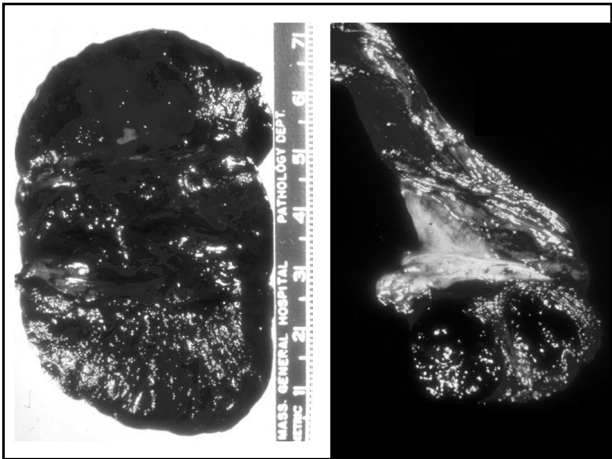
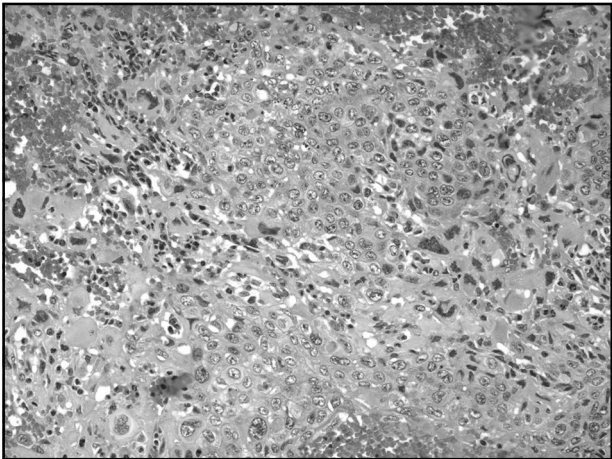
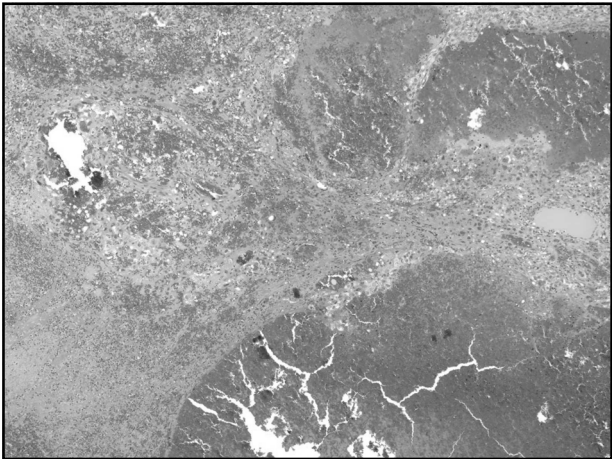
1. **Pierre Masson – 1946**
2. **Robert E. Scully – 1961**
3. **Juan Rosai - 1969**

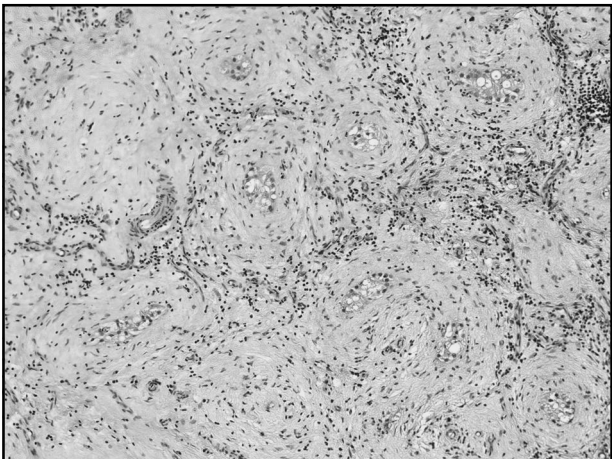
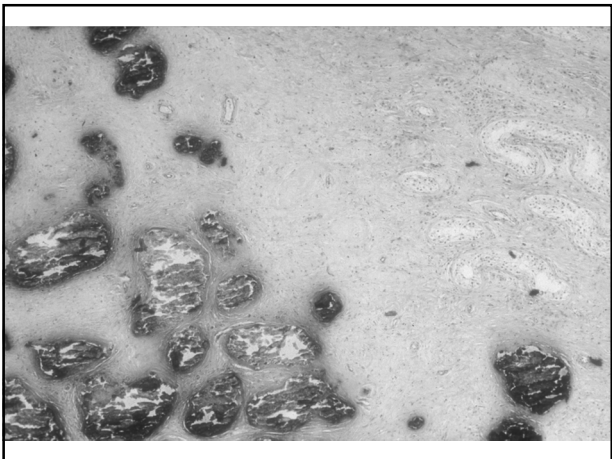
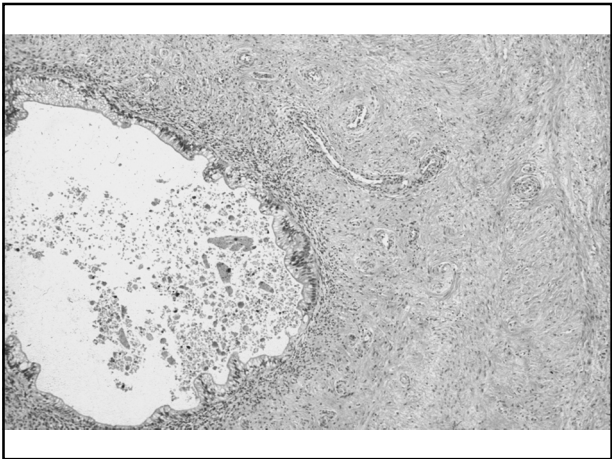
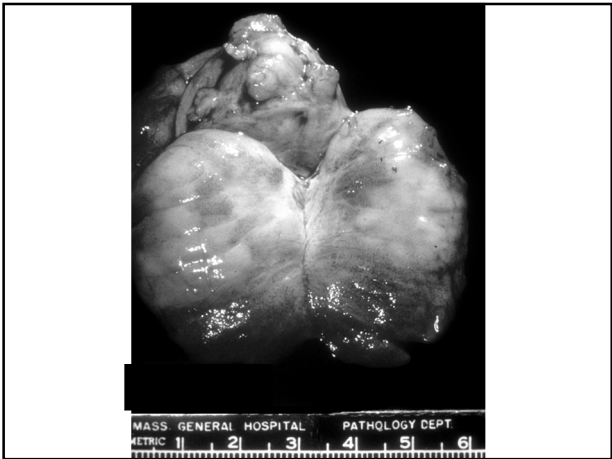
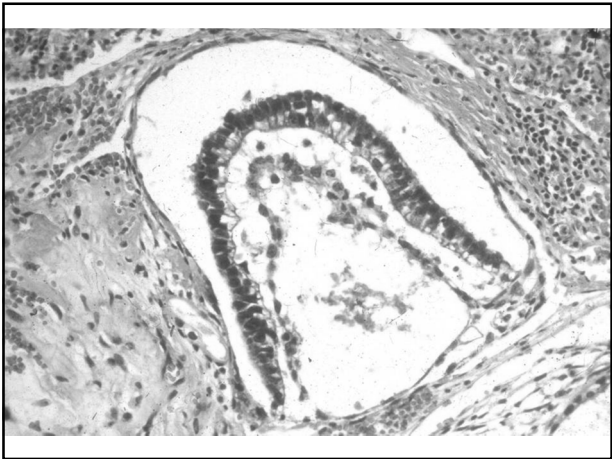
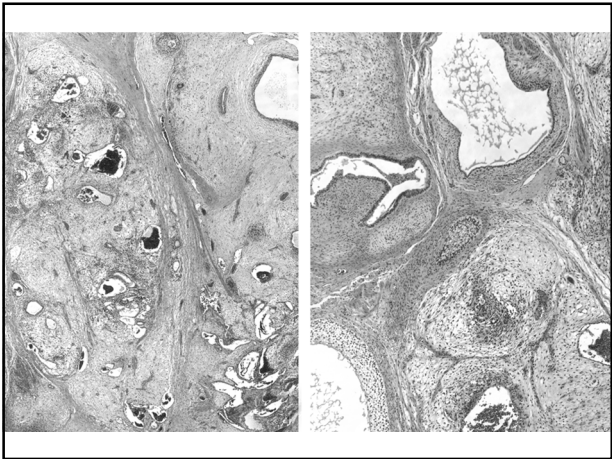


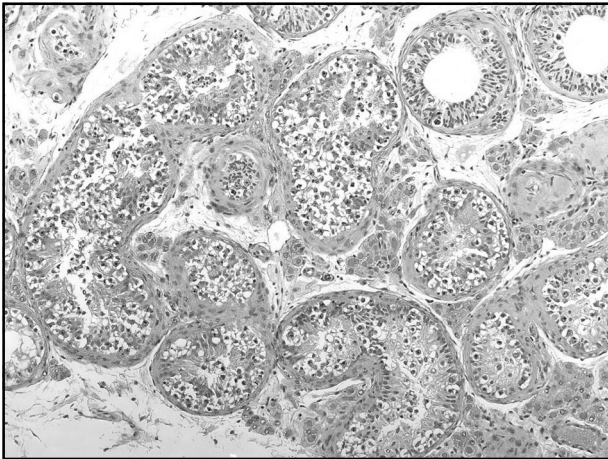
Spermatocytic Seminoma

Always pure
No lymphocytes
No Granulomas
No Glycogen
Unequal, Round Nuclei
Sarcomatous Change





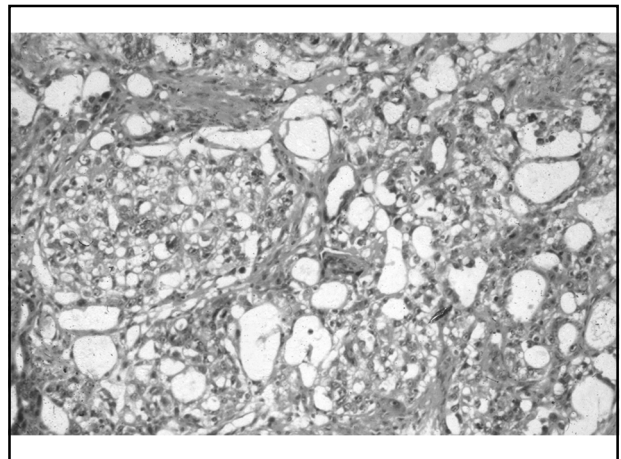
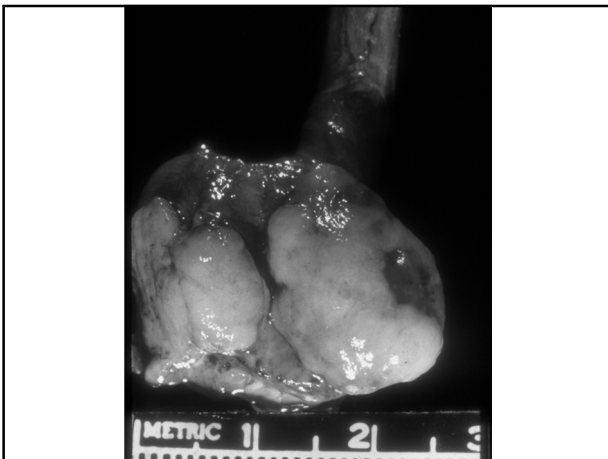




TESTICULAR TUMORS IN CHILDREN

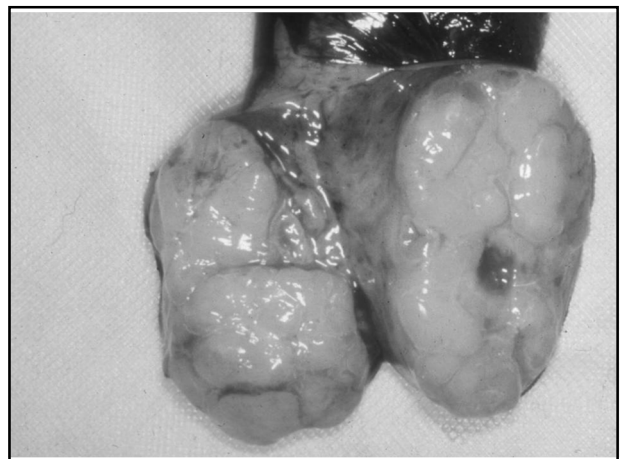
Teratomas	48%
Yolk sac tumor	15%
Epidermoid cyst	14%
Sex cord tumors	13%
Miscellaneous	10%

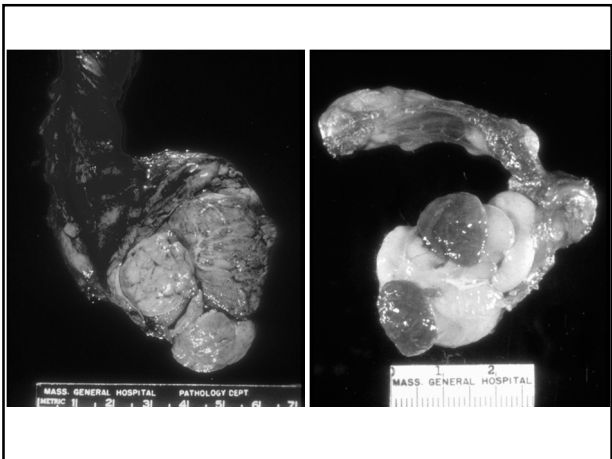
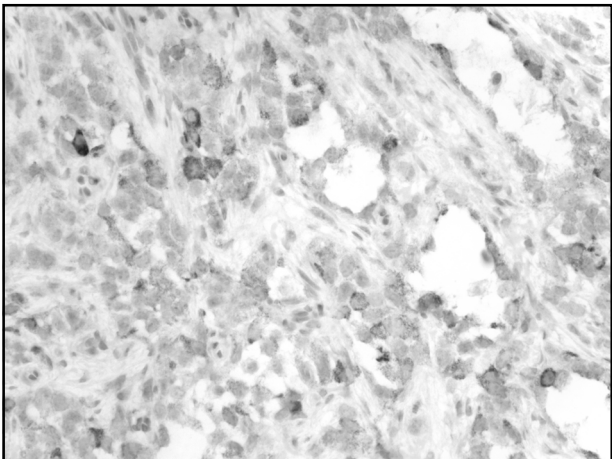
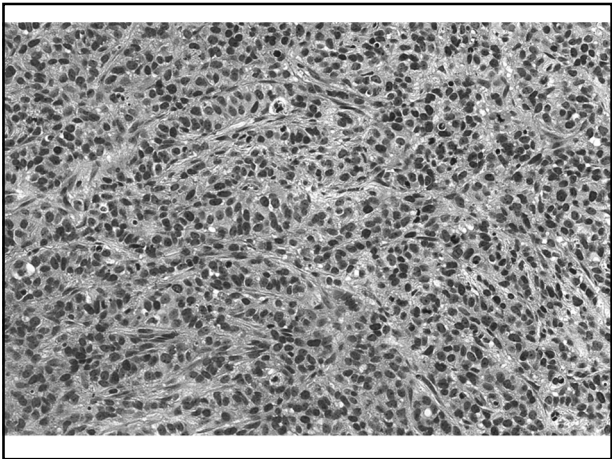
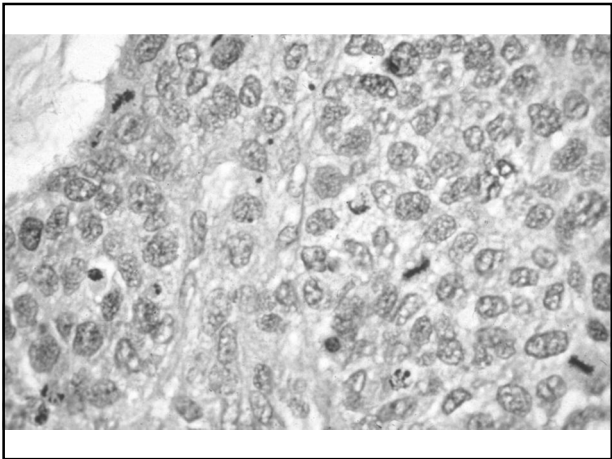
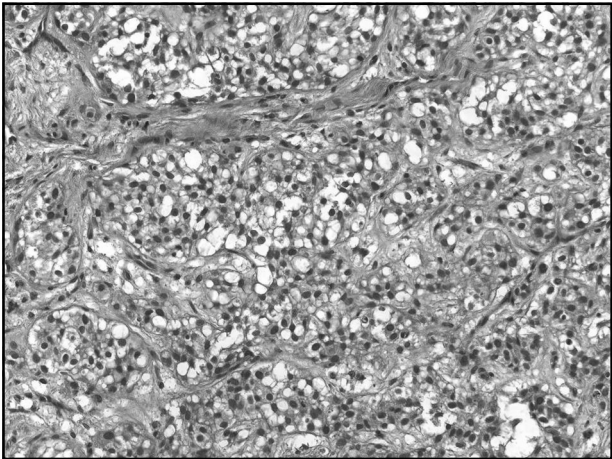
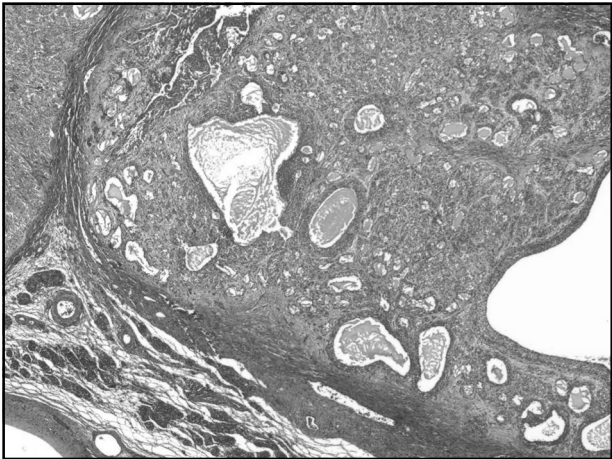
Pohl et al. J Urol 172:2370, 2004

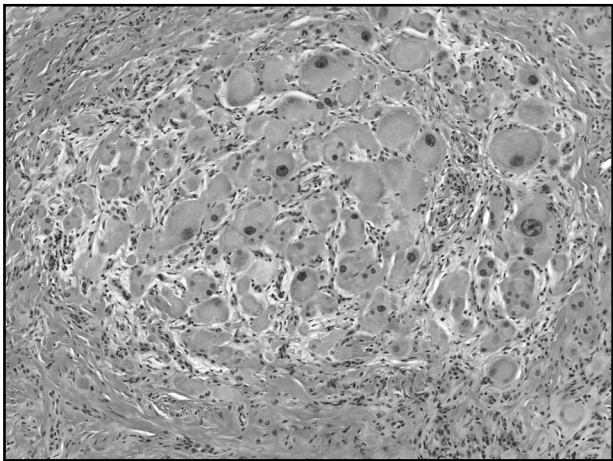
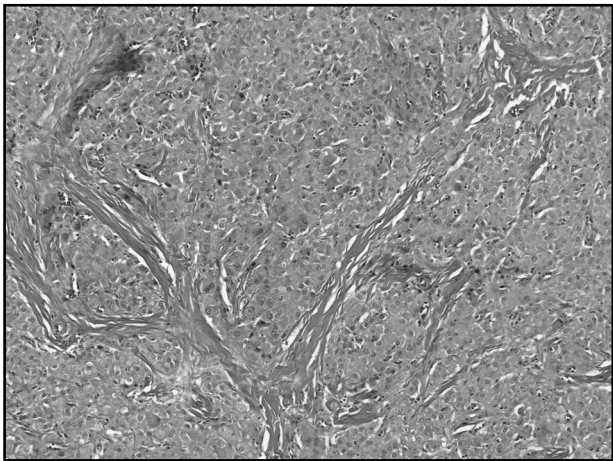
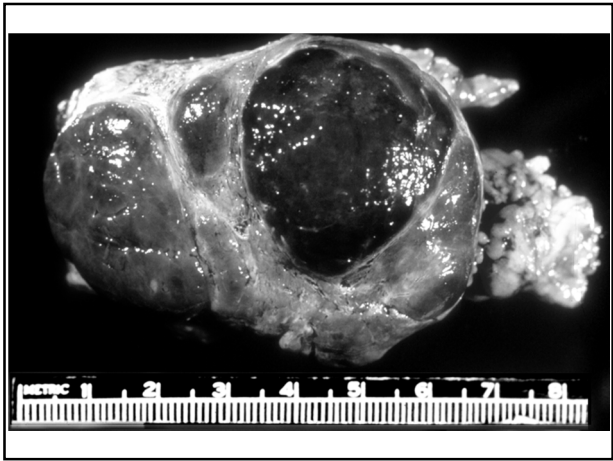
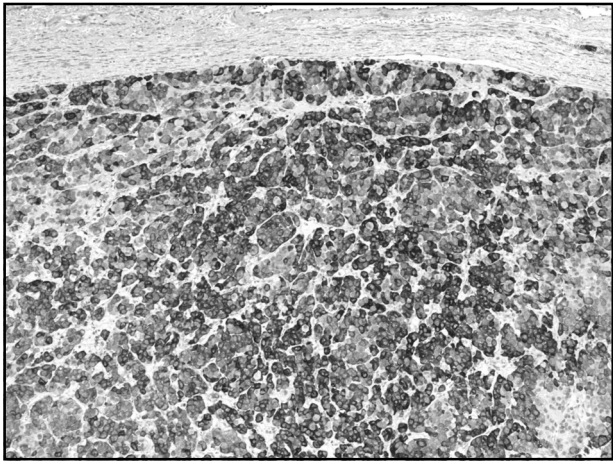
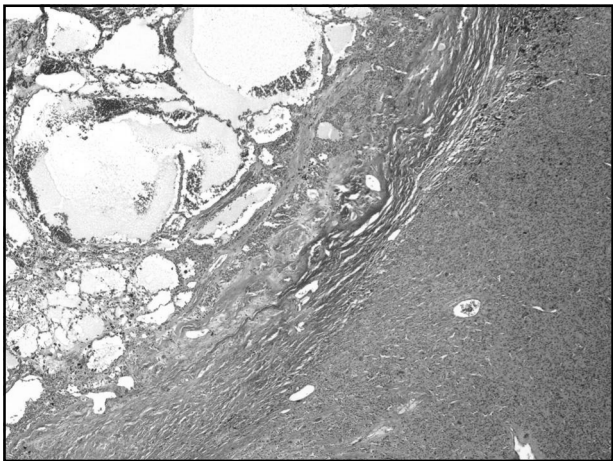
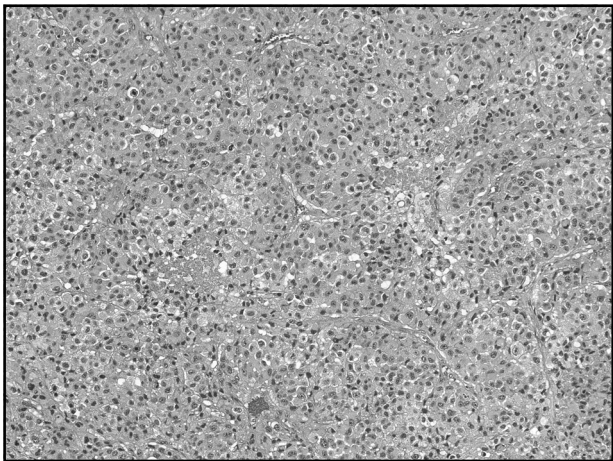


Sex Cord-Stromal Tumors

Leydig cell tumors
Sertoli cell tumors
Sertoli-Leydig cell tumors
Granulosa cell tumors, adult and juvenile
Mixed and unclassified tumors

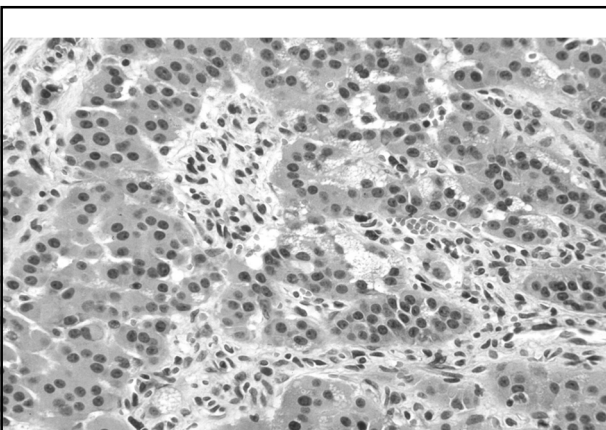
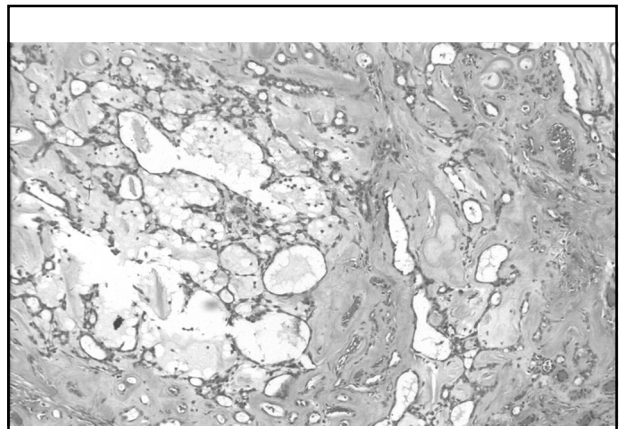
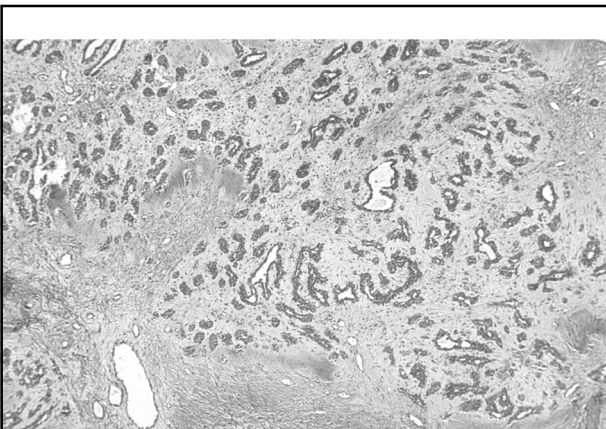
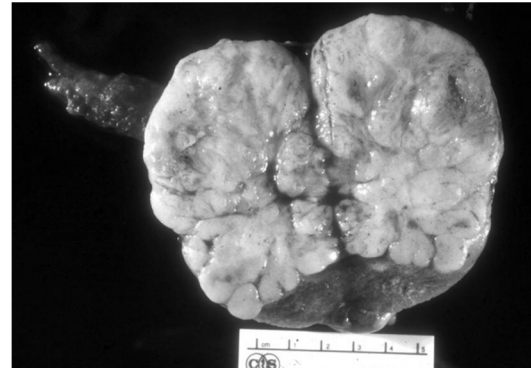


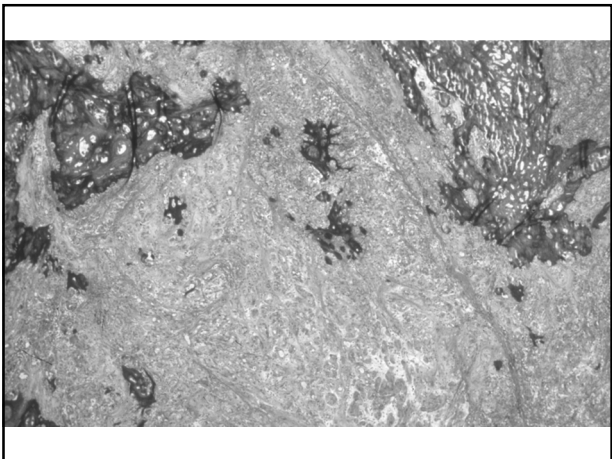
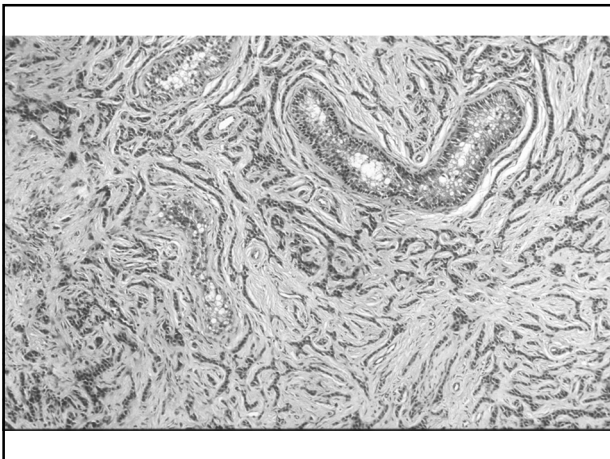
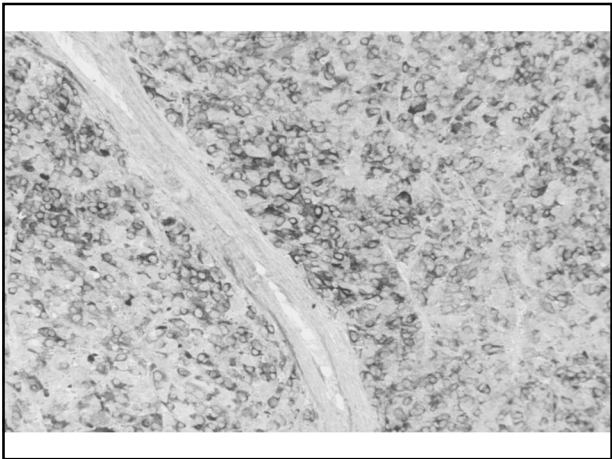
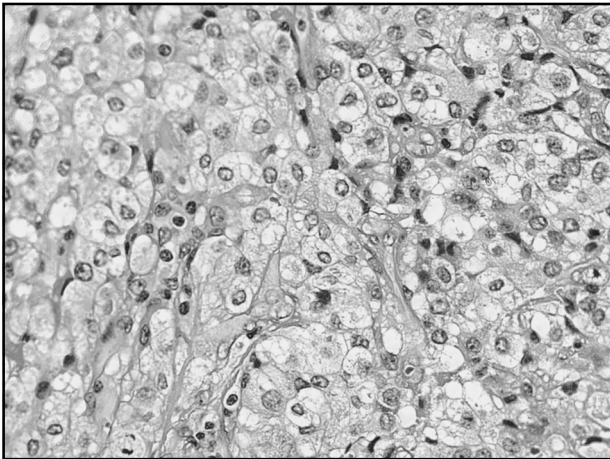
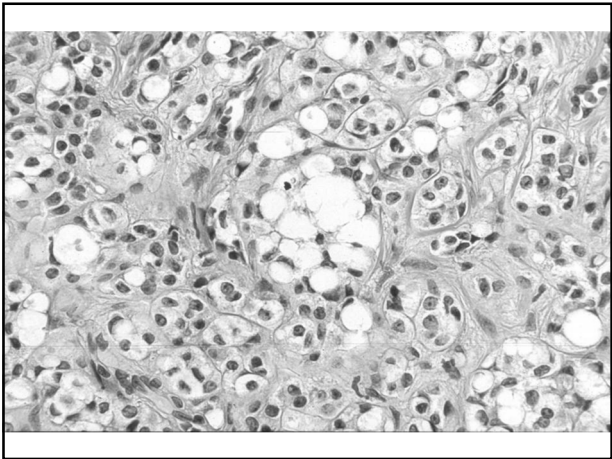
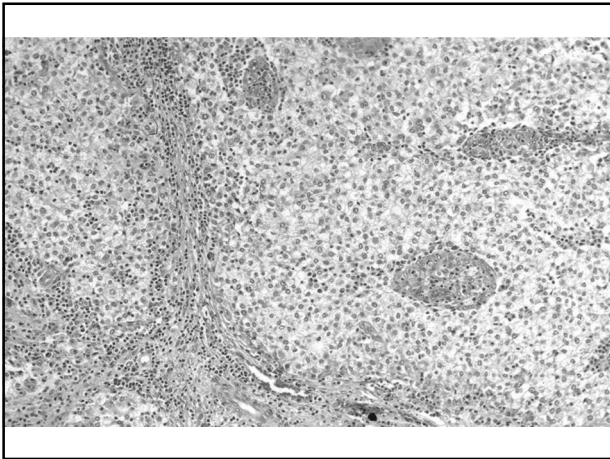




TESTICULAR SERTOLI CELL TUMORS

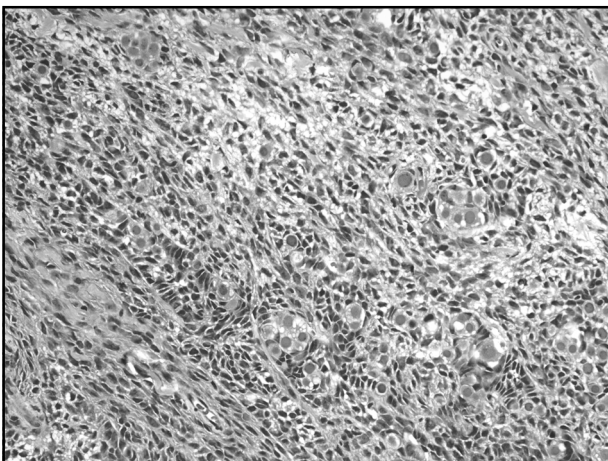
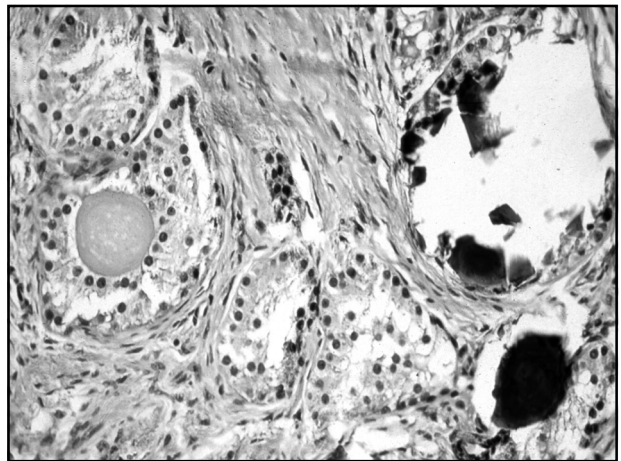
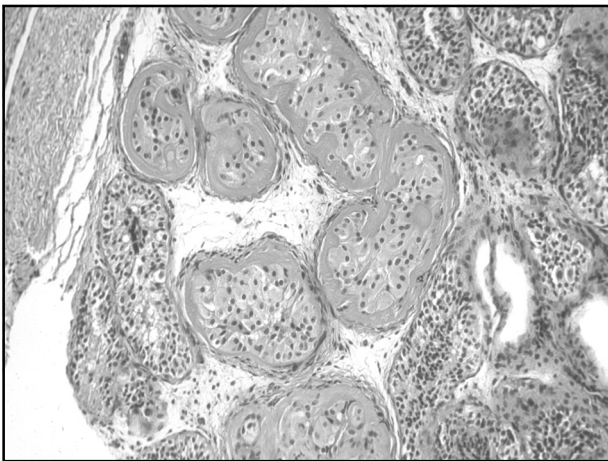
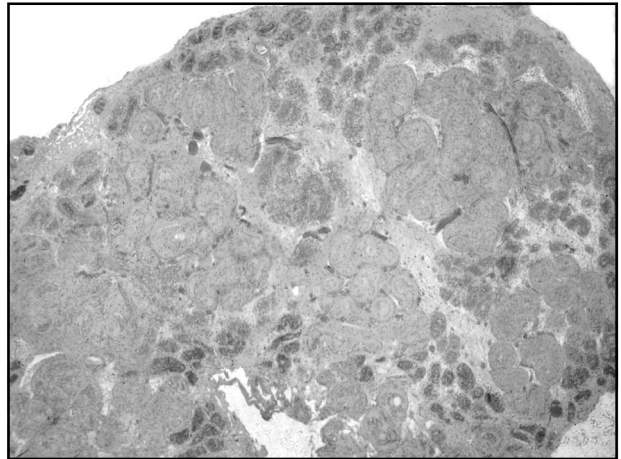
- Sertoli cell tumor, not otherwise specified
- Large cell calcifying
- Sclerosing
- Tumors in Peutz-Jeghers syndrome





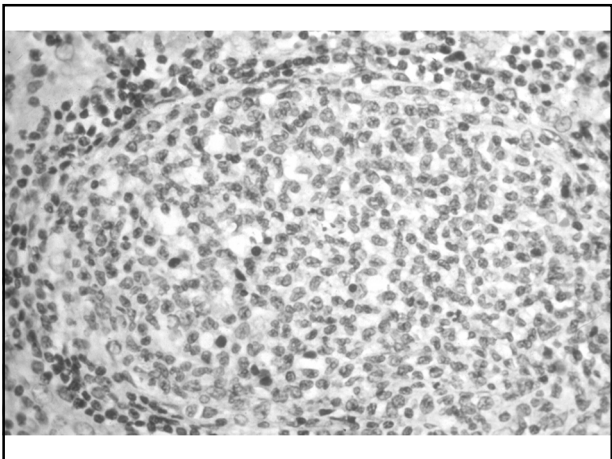
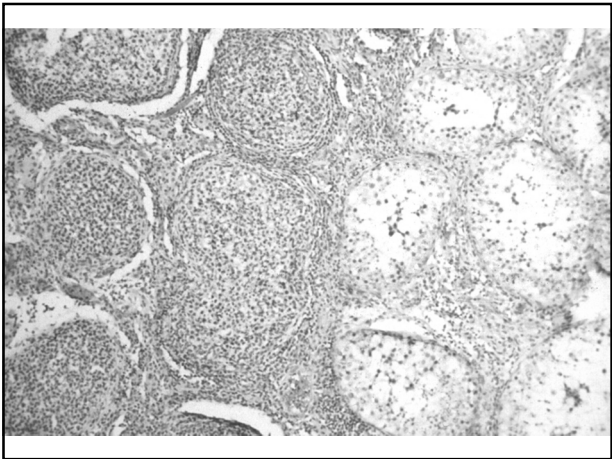
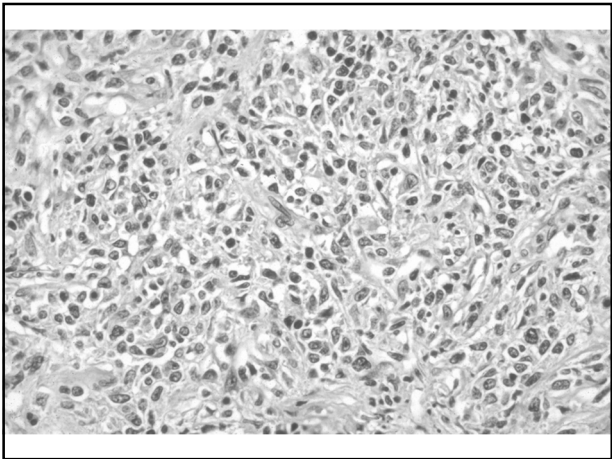
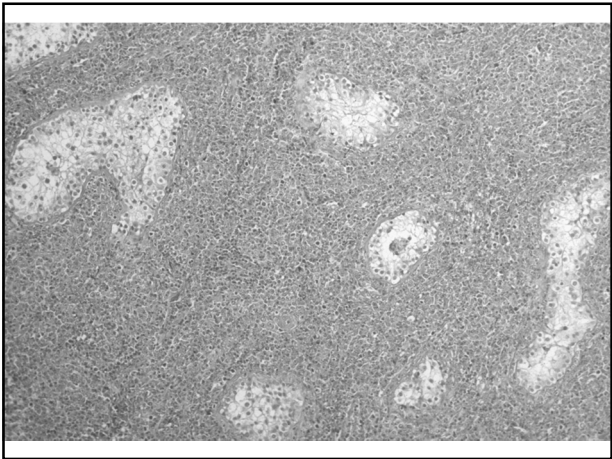
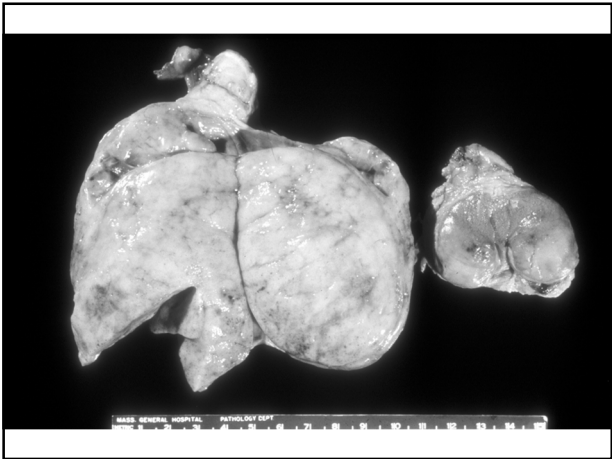
LCCST VS. SCT, NOS

Bilateral	40%
CA++	100%
Intratubular	50%
Large cells, abundant cyto	100%



Testicular Tumors in the 50 + Age Group

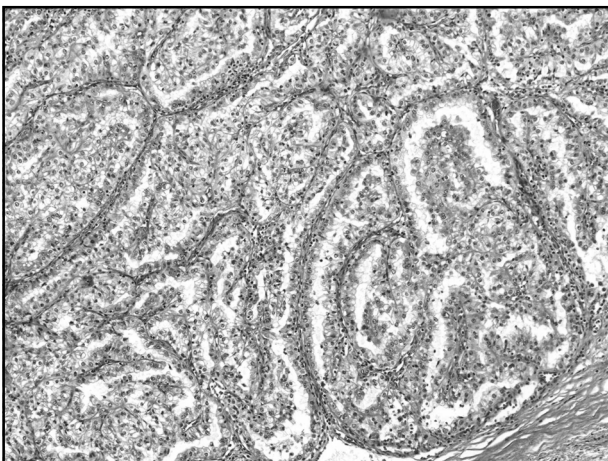
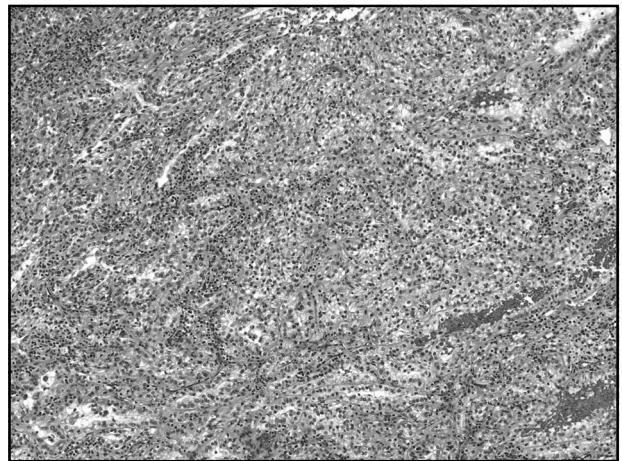
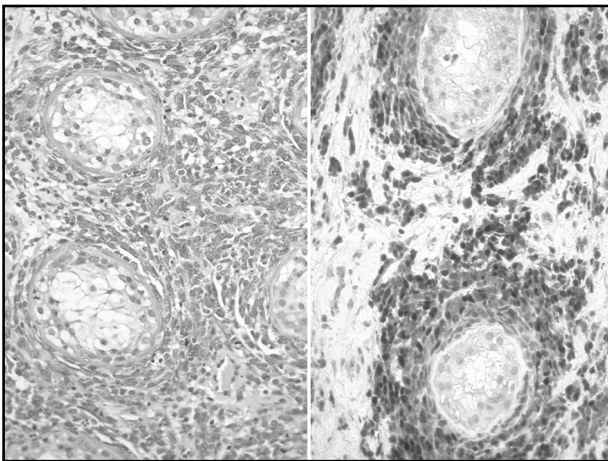
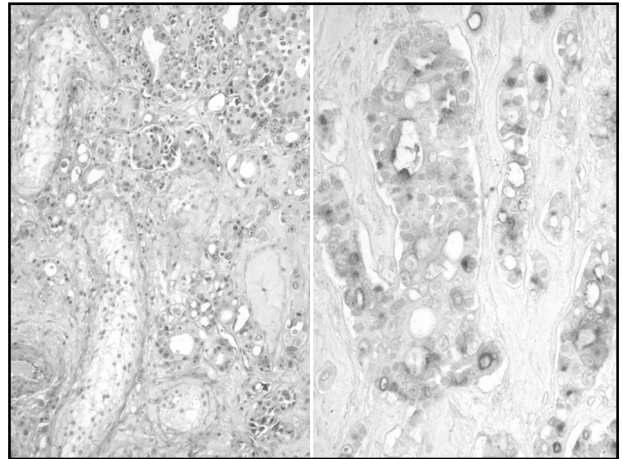
- Lymphoma
- Metastases
- Spermatocytic Seminoma



Mets To Testis	
Symptomatic	15%
Presenting Symptom	4%

Mets To Testis

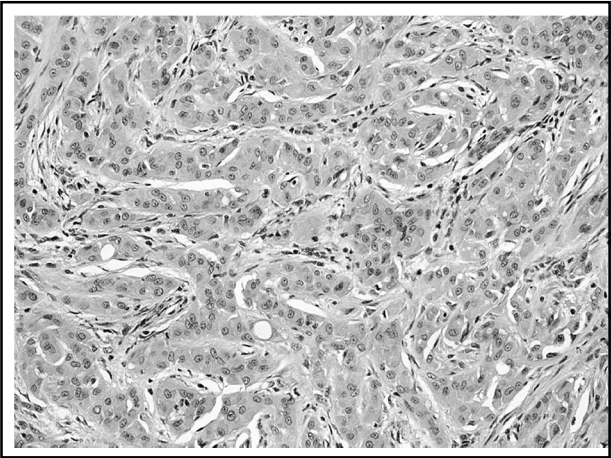
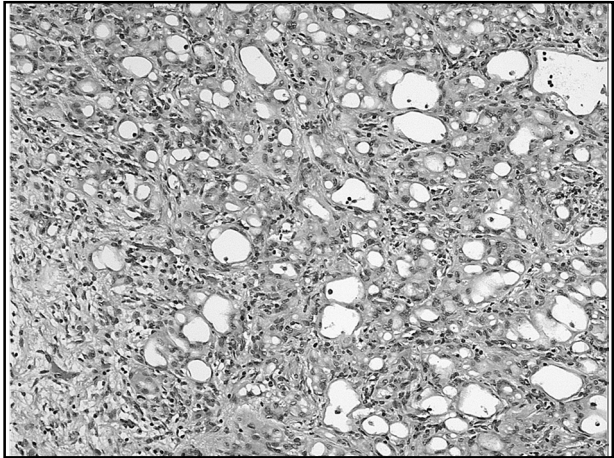
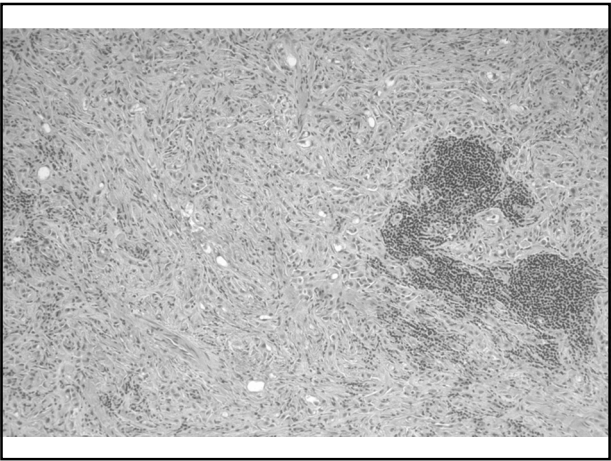
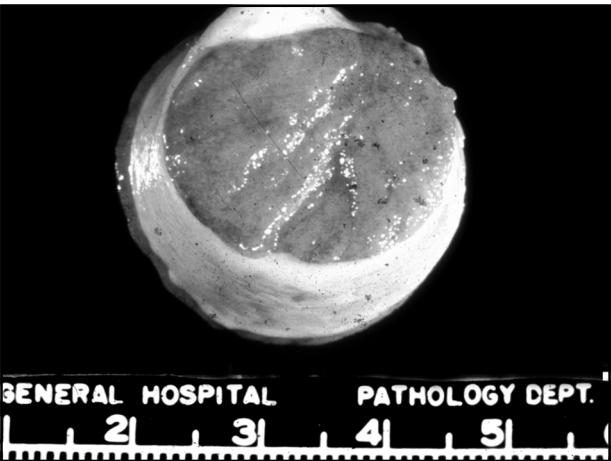
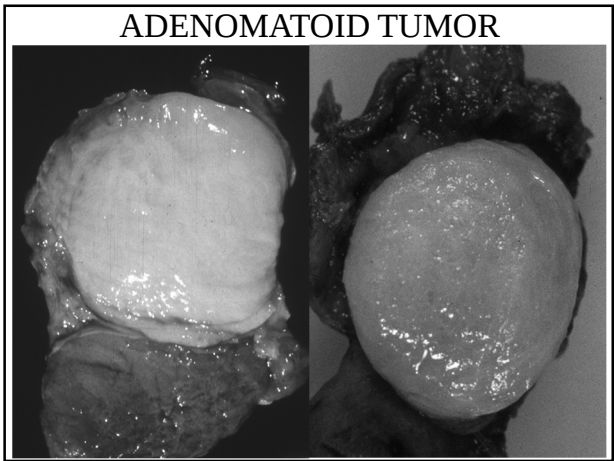
• Prostate	43%
• Lung	15%
• Colon	10%
• Kidney	10%
• Stomach	7%
• Melanoma	4%
• Misc.	11%



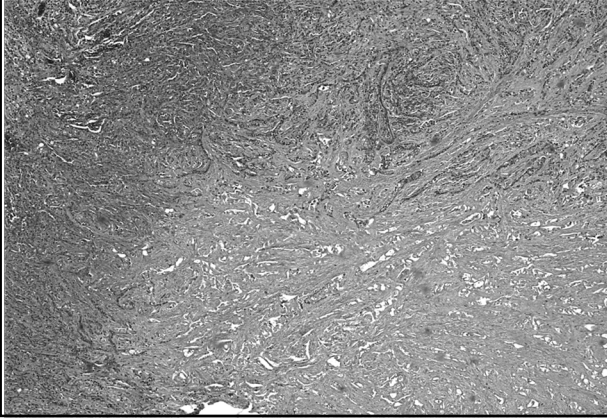
Paratesticular Tumors

Sertoliform rete
cystadenoma
Rete carcinoma
Adenomatoid tumor
Malignant mesothelioma
Mullerian carcinomas

ADENOMATOID TUMOR



INFARCTED ADENOMATOID TUMOR

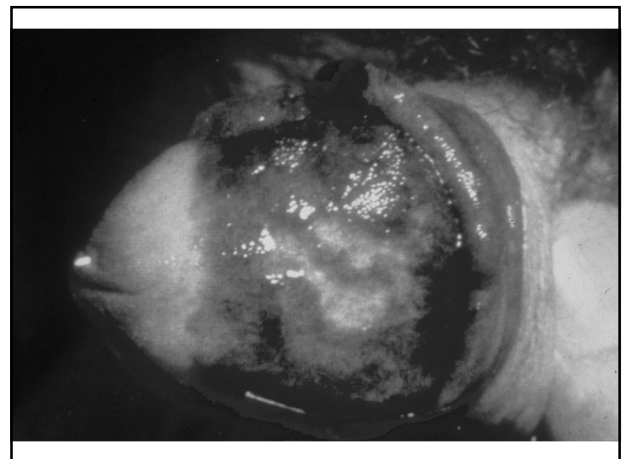
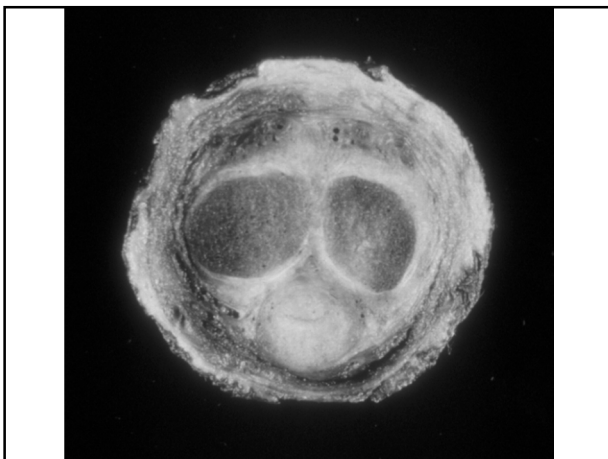
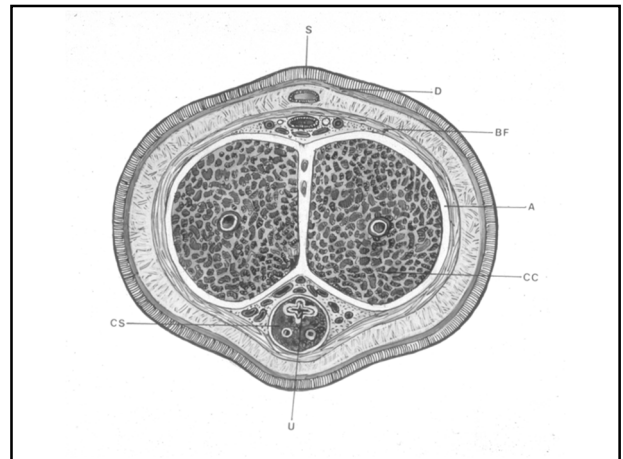
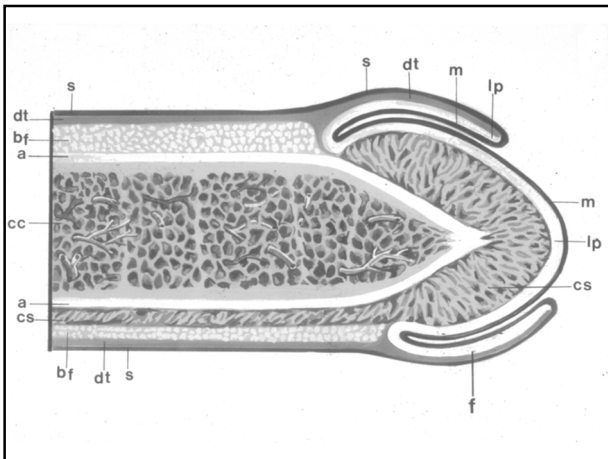


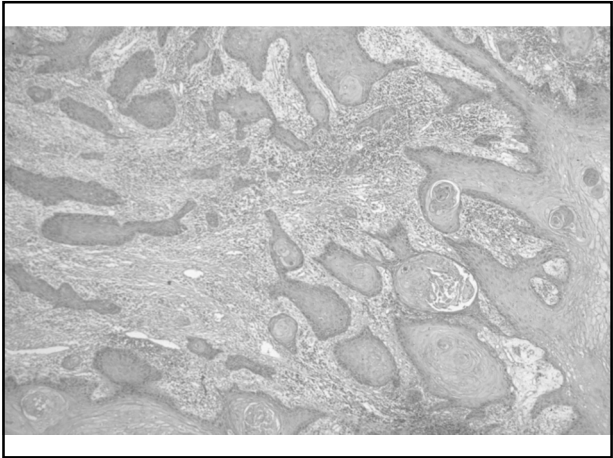
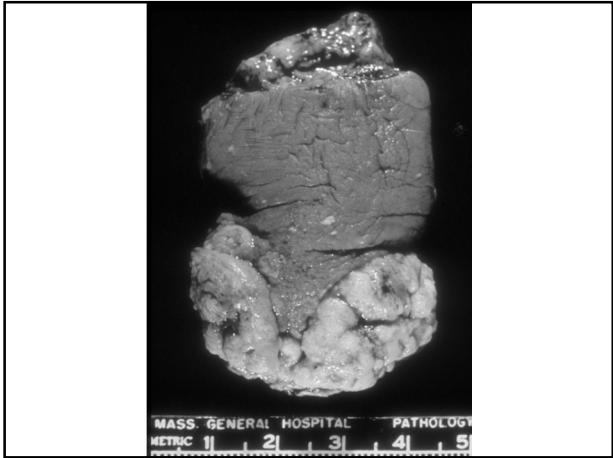
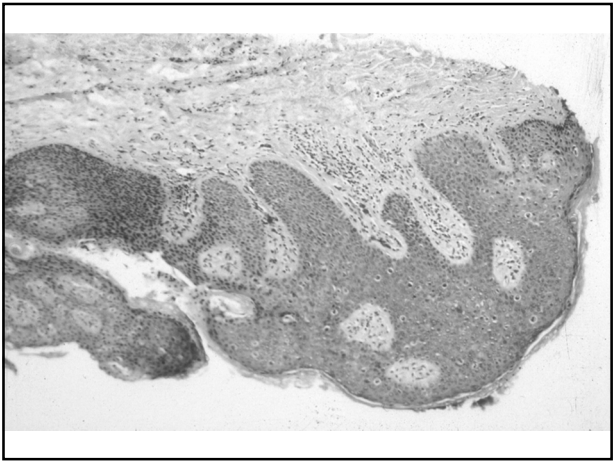
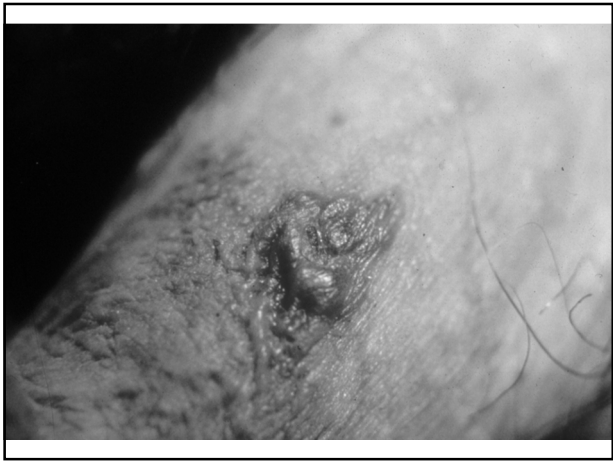
Pathology of the Penis

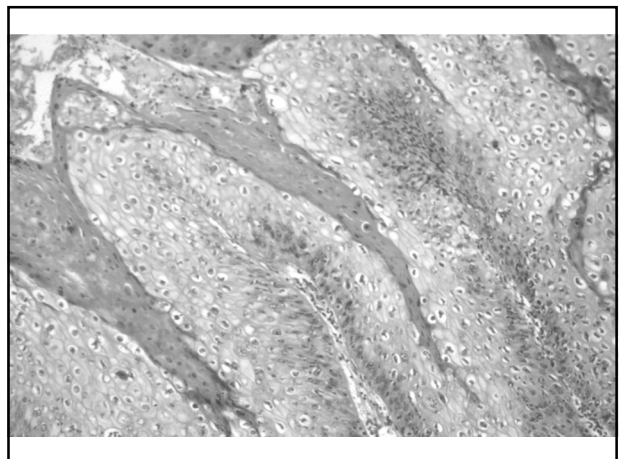
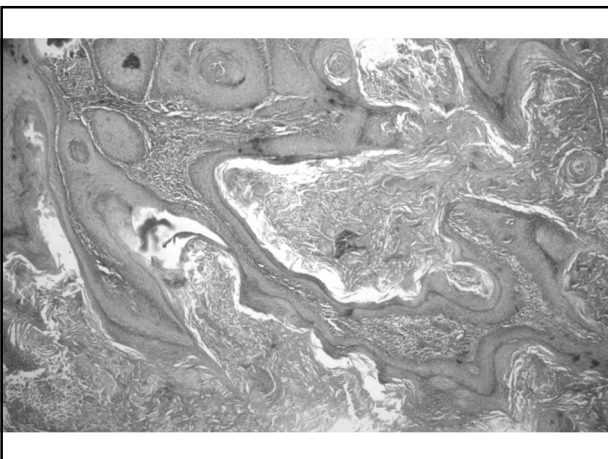
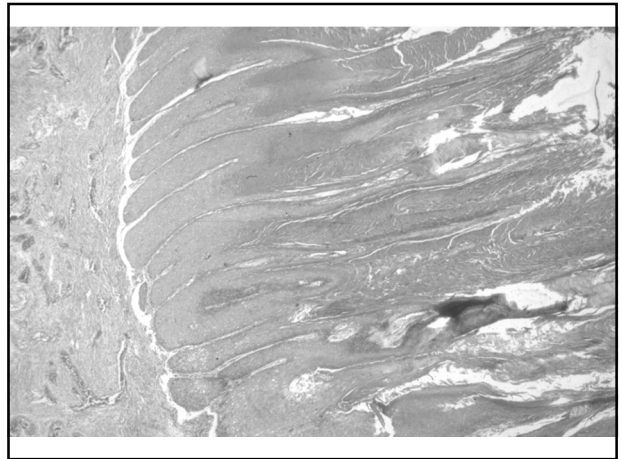
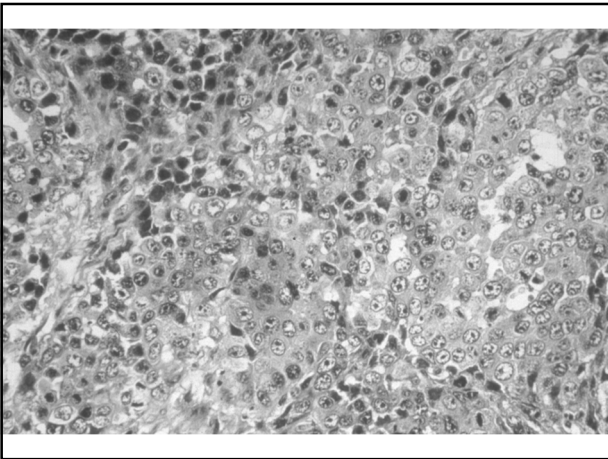
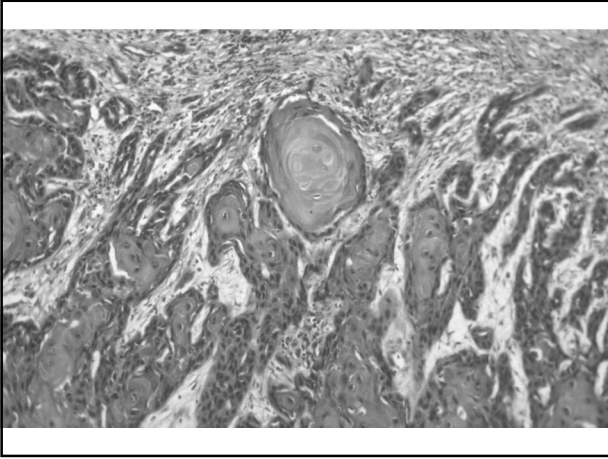
Dr R H Young

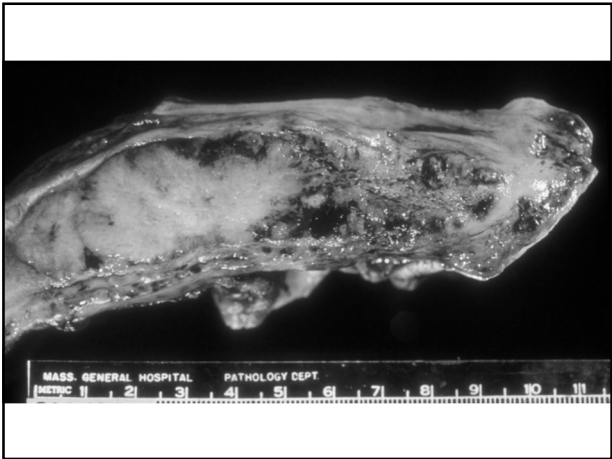
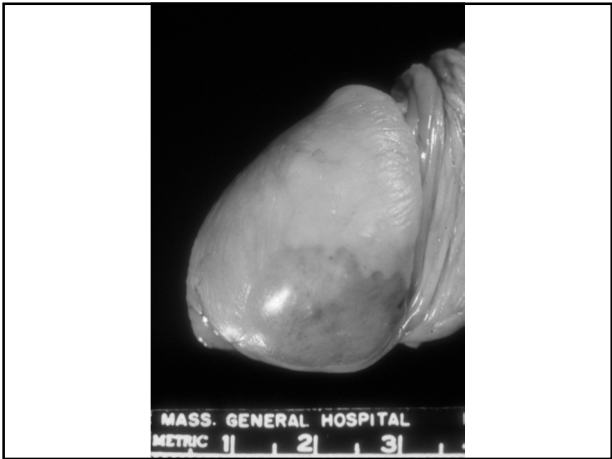
Disclosure Statement

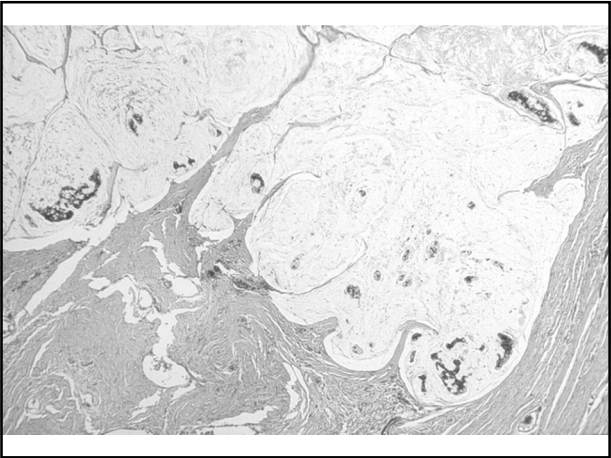
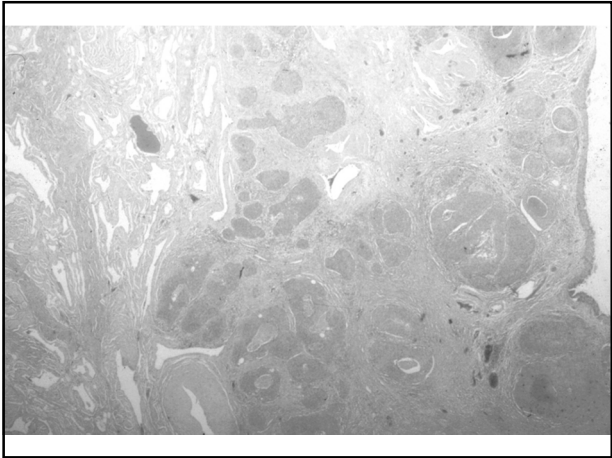
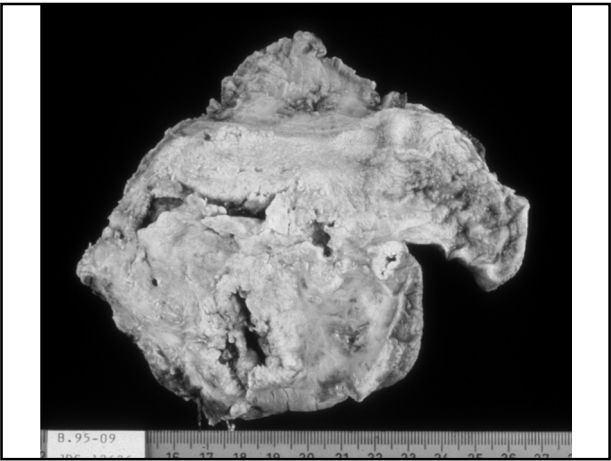
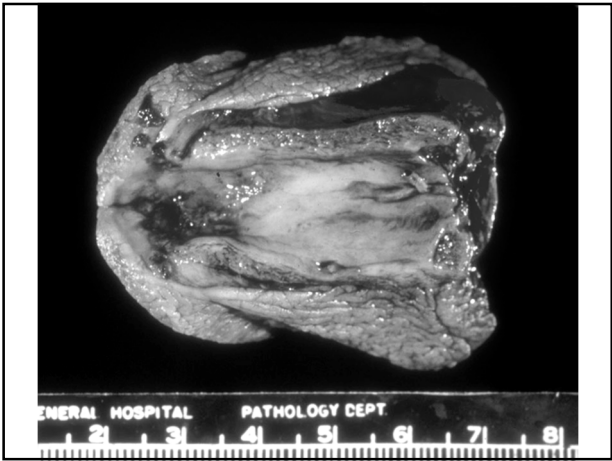
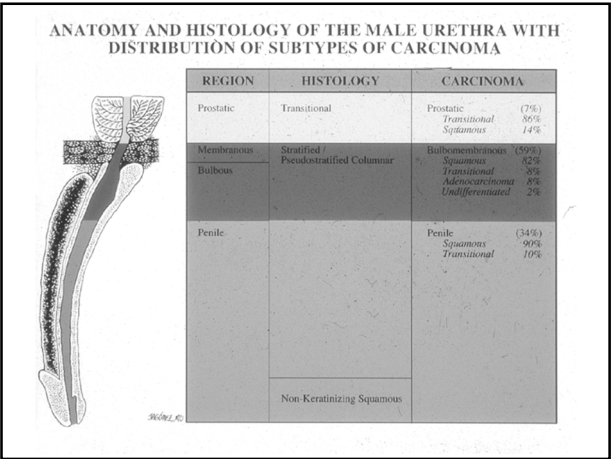
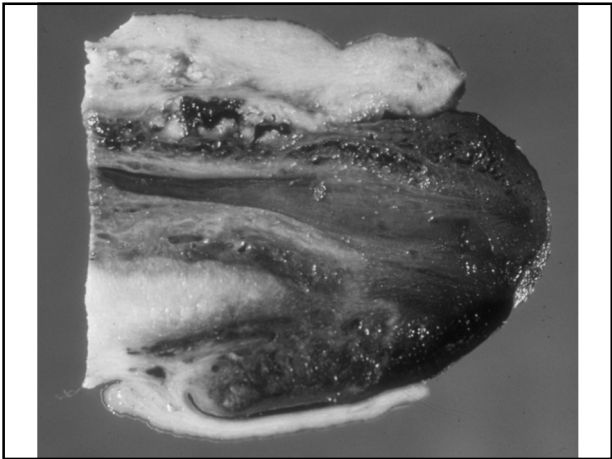
- Nothing to disclose

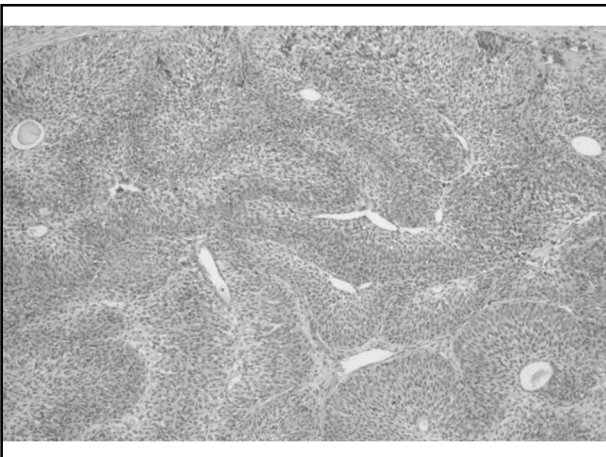
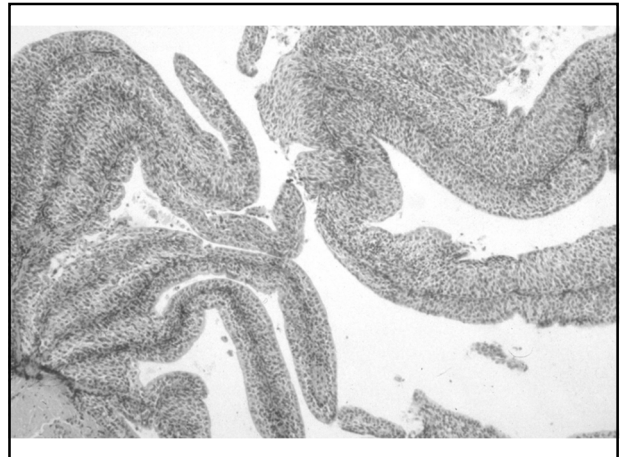
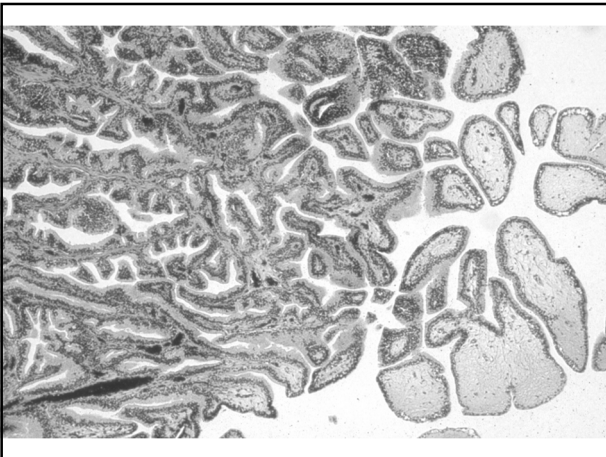
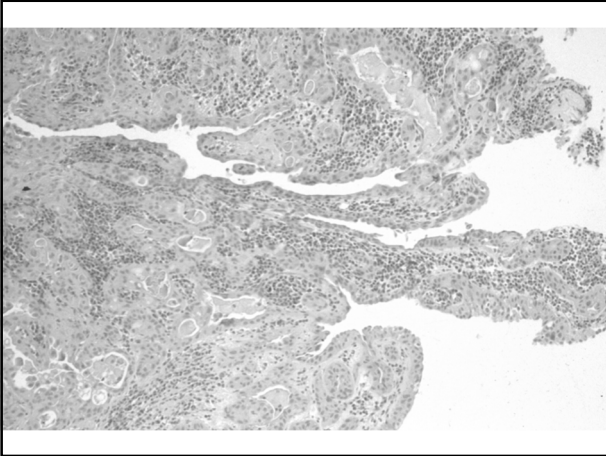














Urologic Emergencies

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Associate Professor of Urology, Fox Chase Cancer Center
Philadelphia, PA



2018 @JSimhan
Urologic Emergencies



Disclosure Statement

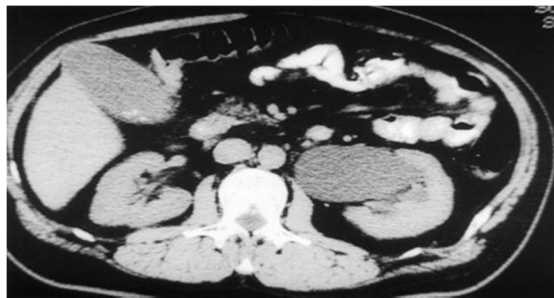
- *Nothing to Disclose*



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Urologic Emergencies



Upper Urinary Tract Obstruction



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Urologic Emergencies



Causes

Table 10.1. Etiology of upper urinary tract obstruction

Intrinsic
Urothelial carcinoma
Fibroepithelial polyp
UPJ obstruction
Ureterovesical junction obstruction
Acquired stricture
Congenital stricture
Urinary stones
Tuberculosis
Papillary necrosis
Trauma
Extrinsic
Renal cell carcinoma
Wilms tumor
Cystic renal diseases
Parapelvic cysts
Renal artery aneurysm
Retroperitoneal malignancy (primary or metastatic)
Adnexal mass
Endometriosis
UPJ obstruction
Retrocaval ureter
Abscess
Appendicitis
Inflammatory bowel disease
Trauma (ureteral ligation)
Radiation therapy
Lymphocele
Urinoma
Retroperitoneal fibrosis
Pelvic lipomatosis
Aortic aneurysm
Pregnancy



Presentation

- *Flank pain, LQ pain +/- fever*
- *Decreased UOP (usually only in bilateral, dehydration or CKD)*
- *LUTS (with distal stones)*



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Urologic Emergencies



Workup

- *CT renal colic*
- *KUB if stones present prior to d/c (ESWL v URS)*
- *UA/Urine Culture (Every Patient)*
- *CBC,BMP*
- *Vital Signs*



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Urologic Emergencies



Treatment

- ***Emergent Stent or PCN***
 - *Hydronephrosis and fever >38.0*
 - *Hydronephrosis and bacteriuria (cath specimen in women)*
 - *Hydronephrosis +SIRS symptoms (hypotension, tachy >120, ect.) PCN for unstable patients*
 - *Bilateral stones with bilateral Hydronephrosis*
 - *Solitary kidney with Hydronephrosis*

Treatment

- ***Other patients that may require sub-acute treatment (usually admission and treat w/in 1 week)***
 - *Hydronephrosis and decreased GFR*
 - *Poor pain control/intractable nausea/vomiting*
 - *High grade obstruction >4 weeks.*

Treatment

- ***Non-infected obstructing stones w normal contralateral kidney***
 - *Doxazosin/flomax, urinary strainer*
 - *May give toradol if Cr w/n/l*
 - *Get KUB and CT renal colic in ED*
 - *F/U with outpatient urologist*
 - *Send urine culture , do not treat with Abx*

Treatment

- ***Non-obstructing stones (No Hydronephrosis)***
 - *Referral to outpatient urologist*
 - *Treat UTI with PO abx if present*
 - *Get CT and KUB in ED prior to D/C*

Case Examples

- ***32 Female with 8mm stone in the lower pole R kidney. No HN on CT scan.***
- ***UA c/w UTI***
- ***No Fevers, +flank pain***
- ***WBC 14, Cr 0.6***

Answer

- ***UTI/Nonobstructing stone***
- ***Get KUB to evaluate for ESWL candidate***
- ***Treat UTI empirically***
- ***Send Ucx.***
- ***Urology referral for next available appointment***

Case Example

- 52 diabetic male with flank pain and fevers to 101F at home, N/V.
- CT with 6mm proximal ureteral stone with UA with 25WBC, nitrite +
- WBC 18, Cr 0.8, Gluc 300
- BP 120/80, HR 90

Answer

- Infected/Obstructed Stone
- Urologic consultation
- IV Abx (Vanc/zosyn or Amp/Gent)
- Glucose control
- IVF
- Urgent/Emergent decompression

Case Example

- 42F with L flank pain and fever to 103, lethargy, chills.
- CT scan with 4mm distal ureteral stone with mild/moderate HN.
- BP 83/40, HR 125 in ED

Answer

- Infected/obstructing stone with patient with hypotension/tachycardia >120.
- Emergent urology consultation, IV Abx, IV fluids
- Will get emergent PCN placement by IR and will need admission to ICU.

Case Example

- 32 male with flank pain/N/V x 3 days
- CT with 8mm proximal right ureteral stone with moderate/severe HN
- UA with 6wbc, nitrite -, 20rbc
- BP 125/77, HR 65
- WBC 16, Cr 1.0
- No fever

Answer

- Non-infected obstructing stone
- If pain controlled in ED and tolerating PO
- KUB prior to d/c, Ucx
- Urologic phone consultation for surgical planning (ESWL v URS w/in 1 month)
- Referral to outpatient urologist w/in 2 weeks.

Penile and Scrotal Presentations



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Penile Fracture

- *“I heard a pop during sexual intercourse”*
- *Patient usually loses erection immediately*
- *“Eggplant deformity”*
- *May have hematuria if urethral injury as well*
- *Needs Urological consultation and penile exploration to avoid permanent ED.*

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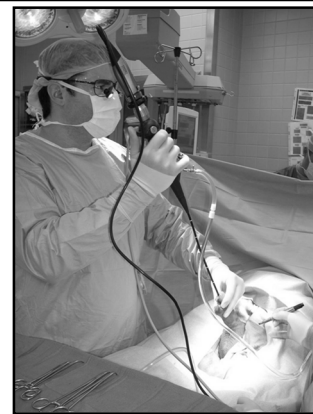
Blood from meatus



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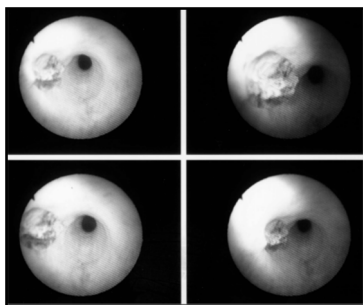


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Penile Fracture

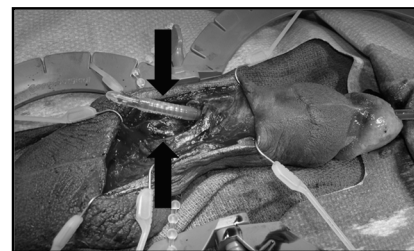


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Penile Exploration



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Corporal Defects Closed



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Urethra Mobilized and Repaired



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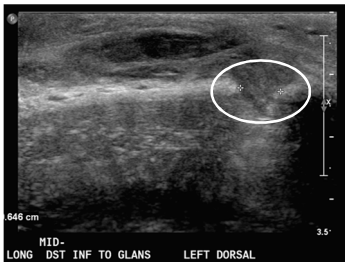
Finished product



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Genital

Clinicians may perform ultrasound in patients with equivocal signs and symptoms of penile fracture. (Expert Opinion)



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How did this happen?

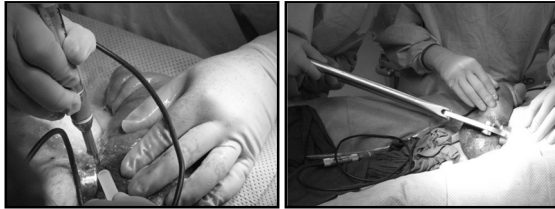


Einstein Urology Titanium penile constriction ring 2018 @JSimhan Urologic Emergencies FOX CHASE CANCER CENTER



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3.5 hours to remove, SPT placed



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Penile Domino/Pearl



If Infected, needs removal in OR.

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Dinosaur Egg???



No, just a 9cm Bladder Stone

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What we can't miss!

- 50 yo man admitted to Internal Medicine
- Temp 101.5 °
- WBC 30k, Glucose 365, U/A nl
- Crepitus on Exam
- What should we be concerned about?



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Fournier's Gangrene

- Necrotizing Fasciitis of the scrotum, perineum, penis, ect.
- Surgical emergency
- If Crepitus, no need for imaging, straight to OR
- May get CT scan or U/S if borderline presentation and no crepitus.
- Tight glucose control, IV Abx, IVF
- Mortality historically 25% (???)

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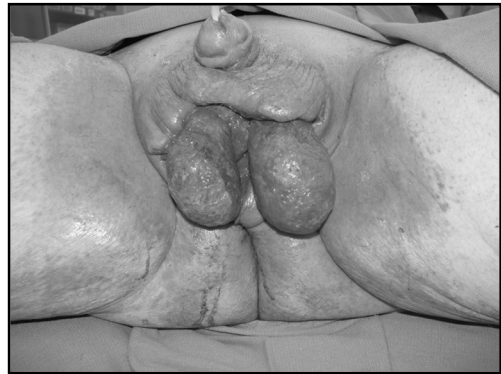
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Fournier's Gangrene

- Many times urologic and general surgery consultation needed. If only scrotal/penile ->urology.
- If only perianal/perineal, no scrotal involvement ->EGS

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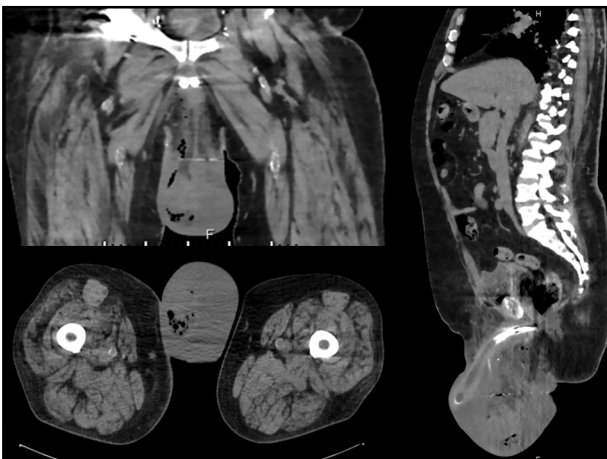
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Case Presentation

- 75M diabetic with a h/o Prostate ca s/p prostatectomy (2003) and inflatable penile prosthesis (IPP, 2003)
- Presents to the ER with scrotal pain, fevers.
- T 38 HR 120 RR 20 BP 123/61 98% RA
- Physical Exam: severe penoscrotal swelling with foul smelling drainage from the perineum
- Wound Cx: Enterococcus, Bacteroides, Blood Cxs: neg

10.3	11.2	132	98	53	275
	174	4.8	22	3.9	

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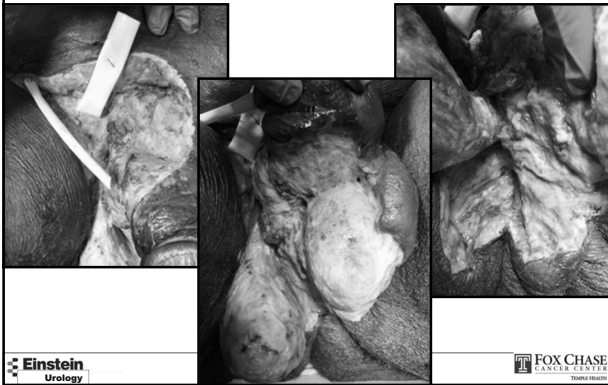


Initial Debridement



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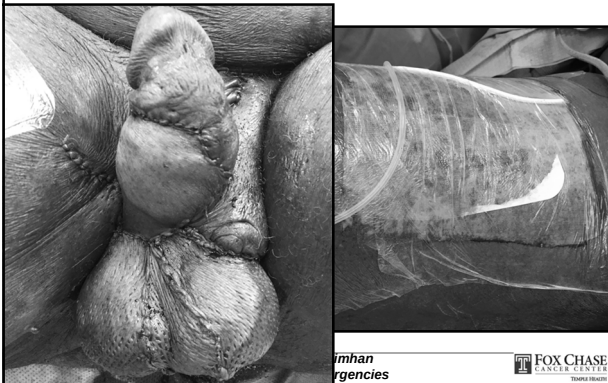
Subsequent Debridements



Granulation Bed – Several Weeks After Debridement



After Skin Grafting



Follow up



Testicular Torsion



Testicular Torsion

- *More common in boys age 12-16, but can happen at any age.*
- *Usual presentation is severe scrotal pain with radiation into abdomen associated with N/V.*
- *May have high-riding testicle with obvious twisting.*
- *Time critical ischemia-8hr window to save the testicle.*

Testicular Torsion

- *If story is classic, no need for imaging.*
- *Urologist needs to be consulted immediately*
- *If UA positive, consider epididymitis and get U/S.*
- *Even if manually detorsed (open book), still needs urgent surgery.*
- *Surgical treatment is scrotal expl, detorsion w orchiopexy v orchiectomy, pex other side.*

Things we can't miss



Testicular Mass
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Testis Mass

- *If concern for testis mass, should get tumor markers (AFP, HCG, LDH), and scrotal U/S.*
- *Typically recommend admitting patients for an inpatient orchiectomy, staging CT scans ASAP as to not risk losing the patient to f/u.*

What is this?



Phimosis

- *Scarring of the uncircumcised foreskin with inability to retract.*
- *Treatment is circumcision or dorsal slit procedure.*
- *Would not force retraction for fear of paraphimosis*
- *If infected (balanitis), may clean with qtip with bacitracin, antifungal. Rarely requires oral Abx.*

How about this?



Or this one?



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Paraphimosis

- A condition where the foreskin gets trapped behind the glans penis.
- Eventually with increased edema, can get ischemia and necrosis of the glans
- Treatment is manual retraction
- If unable to manually retract, urgent urologic consultation is required

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Manual reduction



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Ischemic Priapism

- Prolonged painful erection >4hours.
- Causes- sickle cell, ED medications, meds
- >48 hours increase risk of permanent ED
- Terbutaline (Efficacy unknown)
- Tx irrigation and phenylephrine injection, must be in booth with HD monitoring
- If fails, multiple shunt procedures may be successful
- If shunts fail or >48 hrs, place penile prosthesis

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Irrigation



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The Efficacy of the T-Shunt Procedure and Intracavernous Tunneling (Snake Maneuver) for Refractory Ischemic Priapism

Evangelos Zacharakis, Amr Abdel Raheem, Alex Freeman, Andreas Skolarikos, Giulio Garaffa, Andrew N. Christopher, Asif Muneeb and David J. Ralph*

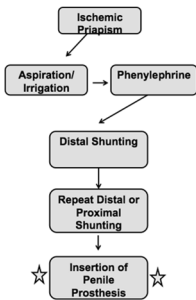
From the Institute of Urology (EZ, AAR, GG, AN, AM, DJR) and the Histopathology Department (AF), University College Hospital (London, United Kingdom), and the 2nd Department of Urology, National and Kapodistrian University of Athens, Athens, Greece (EZ, AS)

THE JOURNAL OF UROLOGY® Vol. 191, 164-168, January 2014 Printed in U.S.A.

- T-shunt loses efficacy with duration of priapism
- After 48 hours of priapism (28 patients)
 - T-shunt successful in only 30%
 - All with necrotic cavernous tissue on biopsy
 - All had severe erectile dysfunction
 - All required penile prosthesis

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Algorithm for Refractory Priapism



Can proceed directly to penile prosthesis insertion if greater than 48 hrs on initial presentation

EUROPEAN UROLOGY 56 (2009) 1033–1038

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

EAU
European Association of Urology

Sexual Medicine

The Immediate Insertion of a Penile Prosthesis for Acute Ischaemic Priapism

David J. Ralph^{a,*}, Giulio Garaffa^a, Asif Muneer^a, Alex Freeman^b, Rowland Rees^a, Andrew N. Christopher^a, Sukbinder Minhas^a

^aSt. Peter's Hospitals and The Institute of Urology, London, United Kingdom
^bDepartment of Histopathology, UCLH, United Kingdom

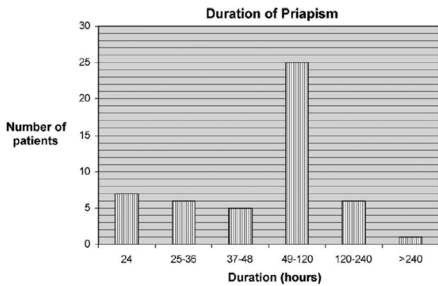
• N = 50

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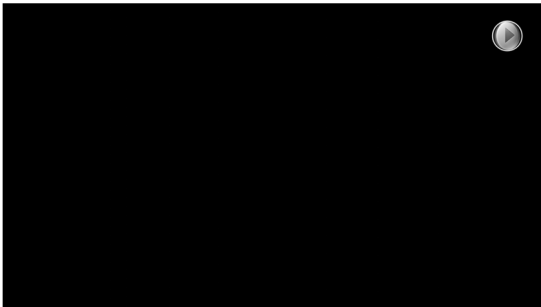
The Immediate Insertion of a Penile Prosthesis for Acute Ischaemic Priapism

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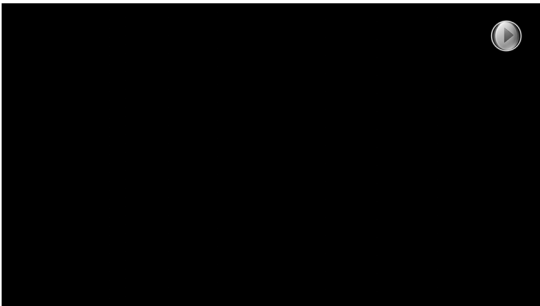
EUROPEAN UROLOGY 56 (2009) 1033–1038



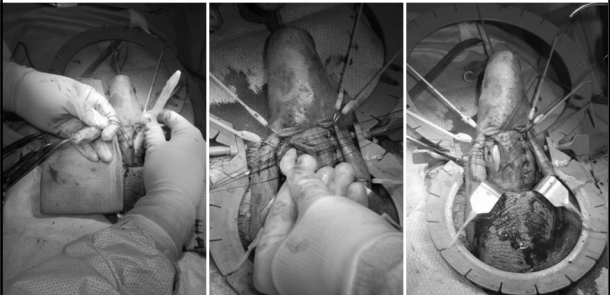
Corporotomy



Corporal Dilation



Prosthesis Insertion



Take Home Messages

- Management of refractory priapism is associated with multiple ED visits and hospital admissions.
- Penile prosthesis is efficacious in treating refractory priapism durably with cost and resource benefits

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Other Urologic Oddities

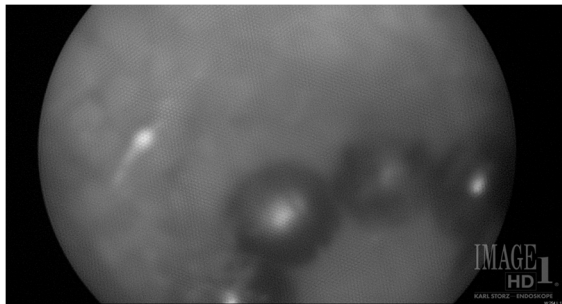


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Foreign Body in the Bladder

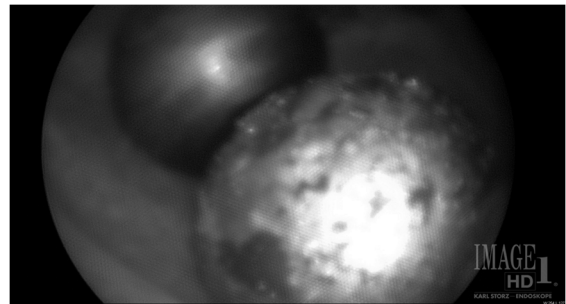


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Intravesical Magnets



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26 male who cut off his own penis with a kitchen knife



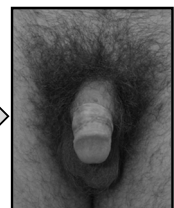
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Penile Amputation

Should perform prompt penile replantation in patients with traumatic amputation, with the amputated appendage wrapped in saline-soaked gauze, in a plastic bag and placed on ice during transport. (Clinical Principle)



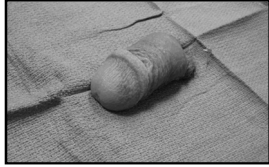
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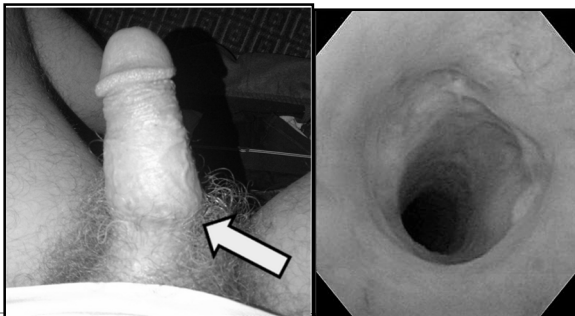
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“Two bag system”

- *Rinse with saline, wrap in gauze and moisten with saline*
- *Place in biohazard bag*
- *Place bag in a saline/ice slush for transport*



s/p Penile Replantation

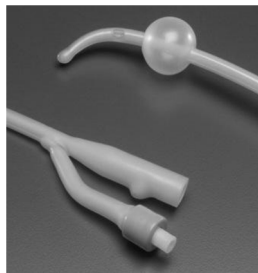


Urinary Retention

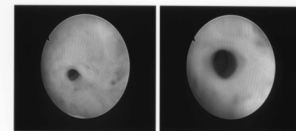
- *Difficulty with urination – often requires Foley catheter.*
- *Most common reasons are urethral stricture disease or BPH*

Coude Catheter

- *Ideal for BPH, difficulty at level of prostate*
- *Balloon port follows curvature*
- *Tip up at 12 'O'clock*
- *“Bigger is better” (18/20F)*



Urethral Stricture



Reconstructive Urology

Urethral Rest: Role and Rationale in Preparation for Anterior Urethroplasty

Ryan P. Terlecki, Matthew C. Steele, Celeste Valadez, and Allen F. Morey

Reconstructive Urology

Urethral Rest: Role and Rationale in Preparation for Anterior Urethroplasty

Ryan P. Terlecki, Matthew C. Steele, Celeste Valadez, and Allen F. Morey

•Frequently referred with:

- ✓ *Indwelling urethral catheter (remove)*
- ✓ *Active regimen of self-catheterization (stop)*
- ✓ *Recent dilation/endoscopic interventions (wait)*

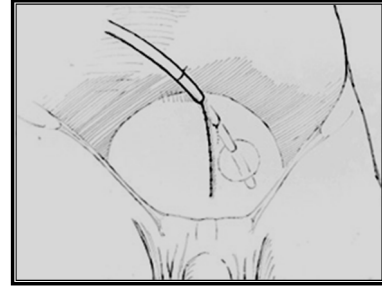
Urology 2011

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Suprapubic Tube Safe, Controlled



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Conclusions

- *Infected/obstructed stones require urgent drainage*
- *Every ER stone patient needs a urine culture*
- *Do not forget the GU exam and make sure foreskin is retracted after foley placements, other manipulations.*
- *Keep your eye out for the time-critical dxs (torsion, Fournier's, priapism, paraphimosis)*

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LASER PHYSICS and SAFETY for UROLOGISTS -



Lori Lerner, MD
Chief, Section of Urology
Associate Professor of Urology
VA Boston Healthcare System
Boston University School of Medicine

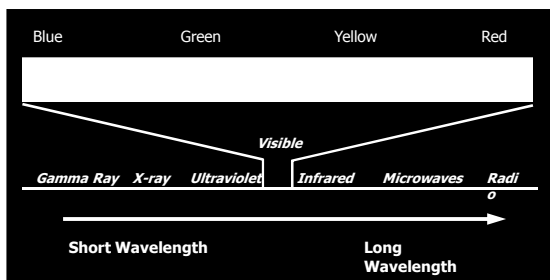
Disclosures

- Consultant and Preceptor for Boston Scientific and Lumenis

What is the goal of most energy sources we use in surgery? What are we trying to do?

Light Amplification by Stimulated Emission of Radiation

ELECTROMAGNETIC SPECTRUM



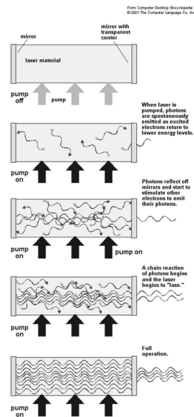
Lasers operate in the ultraviolet, visible, and infrared.

Laser-Professionals.com

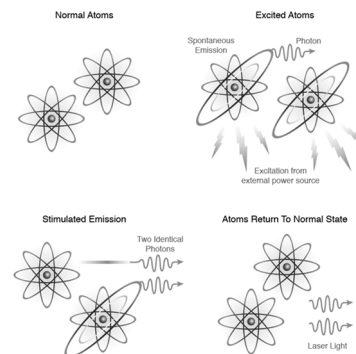
Stimulated Emission

- Outermost electrons of atoms in resting state
- External energy (electricity) raises electron to a higher state
- Emitted photon strikes another atom already at higher state
- As atom returns to resting state it emits photon of energy and wavelength characteristic of the emitting atom
- First photon continues on and second atom releases an additional photon with the same properties of the first

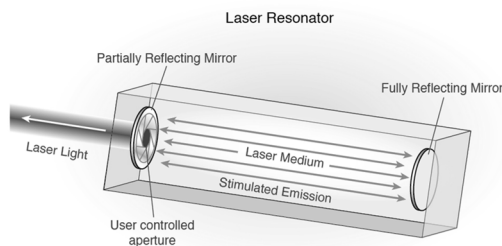
- Emission occurs in active medium of the laser which is contained within the laser resonator
- Active medium can be solid, gas, liquid, or semiconductor
- Laser resonator contains two parallel mirrors, one allows transmission of light and another reflects the atoms back into the resonator causing continued stimulated emission and buildup of energy



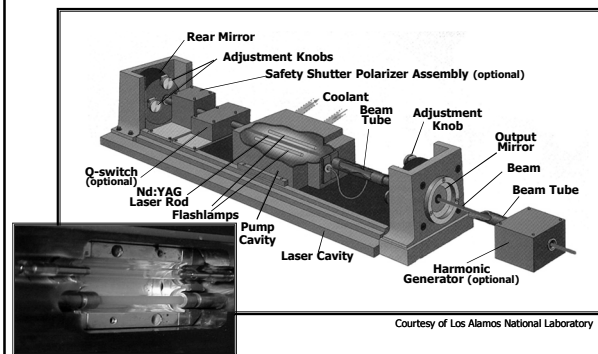
Stimulated Emission



Laser Resonator

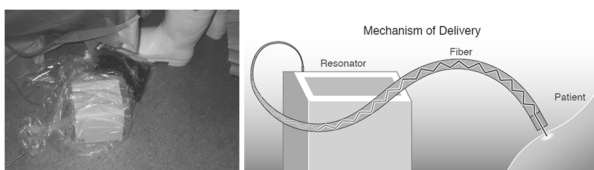


NEODYMIUM YAG LASER



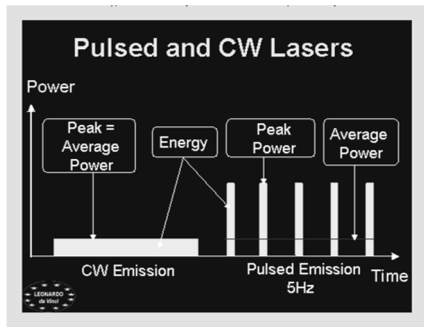
Energy Delivery

- Energy stored and released in a pulsed or continuous fashion, controlled by a foot pedal or switch
- Energy travels along the laser fiber through internal reflection that "bounces" the energy down the fiber



Duration of Laser Emission

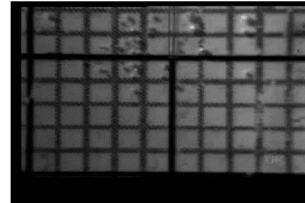
- **CONTINUOUS WAVE** lasers operate with a stable average beam power. In most higher power systems, one is able to adjust the power.
- **PULSED** (normal mode) lasers can be characterized by a set of parameters such as pulse energy, peak power, duration, mean optical frequency and arrival time. Durations are generally few hundred microseconds to a few milliseconds.
- **Q-SWITCHED** laser is a pulsed laser which contains a shutter-like device that does not allow emission of laser light until opened. Energy is built-up in a Q-Switched laser and released by opening the device to produce a single, intense laser pulse.



Pulsed vs Continuous

Holmium – 2140 nm

Thulium – 2013 nm

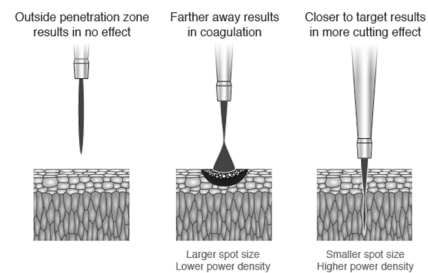


With permission of Lumenis and Lisa Laser

Laser characteristics

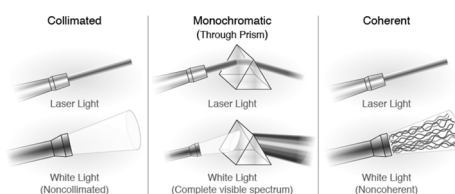
- Energy
 - Expressed in Joules
- Frequency
 - Expressed in Hertz
- Power
 - Rate at which energy is delivered
 - Expressed in Watts
 - Joules x Hertz = Watts
- Power Density
 - Watts per centimeter squared (at target surface)

Power Density



Laser Light Characteristics

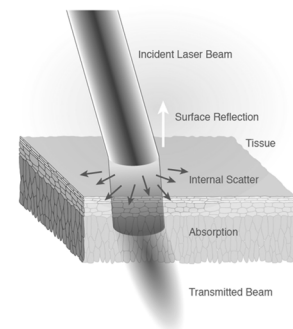
- Nondivergent/collimated (always in parallel)
- Monochromatic (same wavelength)
- Coherent (waves travel in phase)



Laser-Tissue Interactions

- Laser light can:

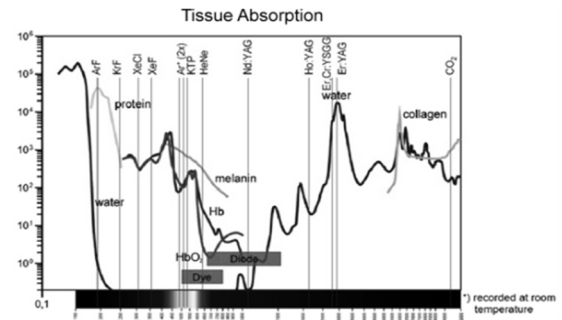
- Reflect
- Scatter
- Transmit
- Absorb



Laser-Tissue Interactions

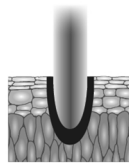
- Absorbed photons raise temperature and destroy cells
- Depth of penetration is distance in which 90% of laser energy deposited
- Wavelength of laser photons affects tissue interactions
- Tissue has different absorption coefficient for each wavelength
- Important characteristics include hemoglobin, pigmentation content and chemical composition

Temp Threshold	Biological Effect
37 °C	Body temperature
45 °C	Hyperthermia
60 °C	Coagulation (near tissue)
100 °C	Vaporization / Cutting (contact with tissue)
150 °C	Carbonization
300 °C	Melting

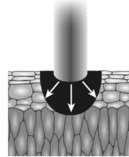


Two Ways Heating Occurs

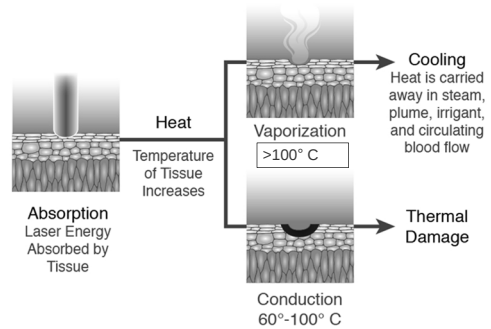
Transmission
Laser instantly heats tissue to a depth determined by the absorption length



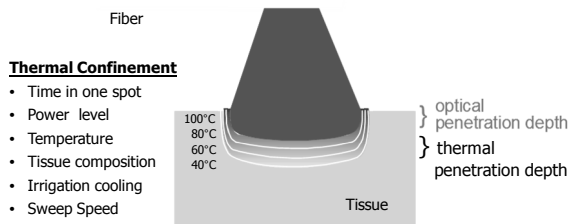
Conduction
Heat flows from region heated by laser into adjacent tissue



Where Heat Goes



Factors in Coagulation Depth

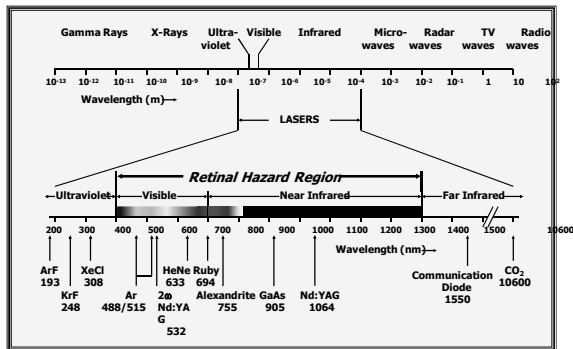


Courtesy of Dr. Alex Te

Laser Safety

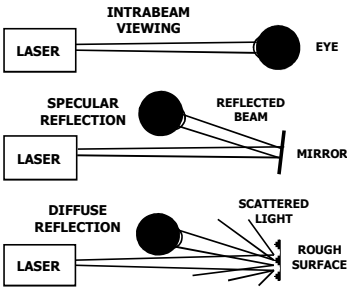
- It is imperative that lasers are used safely – for the patient, surgeon, and operating room personnel.
- Given the different characteristics, different lasers have different safety concerns.
- The most common injuries associated with lasers are skin burns and eye injury, including permanent vision loss.

Laser Spectrum



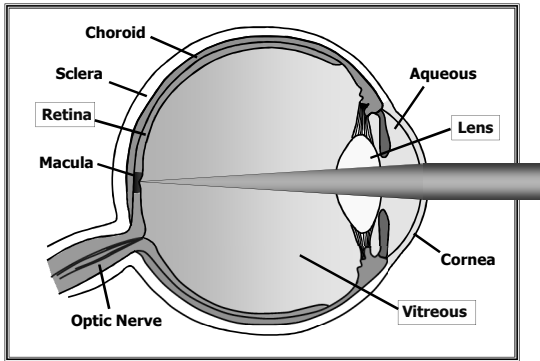
Laser-Professionals.com

Types of Laser Eye Exposure



Laser-Professionals.com

Human Eye



Laser-Professionals.com

Laser Classification Summary

- Class 1** Incapable of causing injury during normal operation
- Class 1M** Incapable of causing injury during normal operation unless collecting optics are used
- Class 2** Visible lasers incapable of causing injury in 0.25 s.
- Class 2M** Visible lasers incapable of causing injury in 0.25 s unless collecting optics are used
- Class 3R** Marginally unsafe for intrabeam viewing; up to 5 times the class 2 limit for visible lasers or 5 times the class 1 limit for invisible lasers
- Class 3B** Eye hazard for intrabeam viewing, usually not an eye hazard for diffuse viewing
- Class 4** Eye and skin hazard for both direct and scattered exposure

- Aversion response may not provide adequate eye protection
- CDRH includes visible lasers only
- ANSI includes invisible lasers
- CW maximum power (visible) 5 mW

Expanded Beam
(Class 2M)



Laser-Professionals.com

CAUTION

Laser Radiation - Do Not Stare Into Beam or View Directly With Optical Instruments

Helium Neon Laser
5 milliwatt max/cw
CLASS IIIa LASER PRODUCT

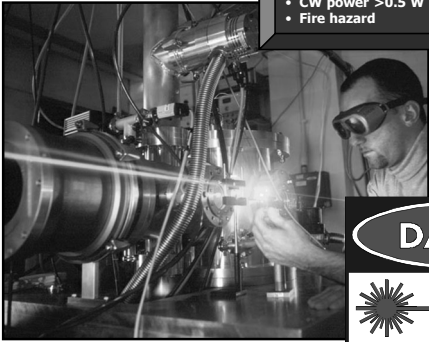
DANGER

LASER RADIATION - AVOID DIRECT EYE EXPOSURE

ND:YAG 532nm
5 milliwatts max/cw
CLASS IIIa Laser Product

CLASS 4

- Exposure to direct beam and scattered light is eye and skin hazard
- Visible or invisible
- CW power >0.5 W
- Fire hazard



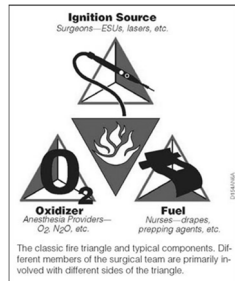
DANGER

VISIBLE LASER RADIATION - AVOID EYE OR SKIN EXPOSURE TO DIRECT OR SCATTERED RADIATION

ND:YAG
Wavelength: 532 nm
Output Power: 20 W
CLASS IV Laser Product

Photo: Keith Hunt - www.keithhunt.co.uk
Copyright: University of Sussex, Brighton (UK)

Class 4 Lasers Can Cause Fires



VA Boston Healthcare System

Laser Safety Standards

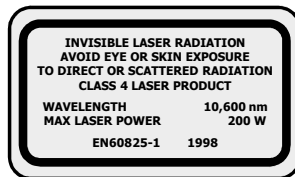
- The Federal Laser Product Performance Standard (FLPPS) of the Center for Devices and Radiological Health (CDRH). This is federal law and applies to the manufacturer of lasers.
- The American National Standard for Safe Use of Lasers (ANSI Z136.1) This is a VOLUNTARY Standard that applies to the use of lasers. It is recognized by The Occupational Safety and Health Administration (OSHA)
- IEC 60825 International Standard

Laser-Professionals.com

International Laser Warning Labels



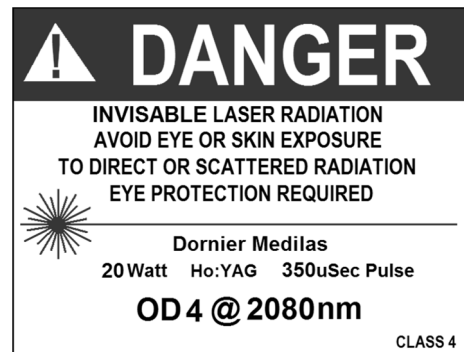
Symbol and Border:
Background: Yellow



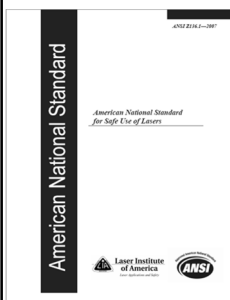
Legend and Border: Black
Background: Yellow

Laser-Professionals.com

VA Boston Laser Sign



Overview of Ansi Z136.1



1. Management appoints laser safety officer
2. LSO verifies laser classification
3. LSO evaluates hazards by determining
Mpe -- od -- nhz
4. LSO specifies control measures
 - Engineering controls
 - Enclosures
 - Interlocks
 - Warning systems
 - Administrative and procedural controls
 - Authorized personnel
 - Sop (including alignment)
 - Training
 - Protective equipment
 - Eyewear
 - Barriers

Laser-Professionals.com

Open Beam Control Measures

Ansi Section 4.3.1.1

- ⚙ Laser Controlled Area
- ⚙ Eye Protection
- ⚙ Beam Control
- ⚙ Administrative and Procedural Controls
- ⚙ Education and Training

Laser-Professionals.com

Laser Safety Eyewear



Laser-Professionals.com

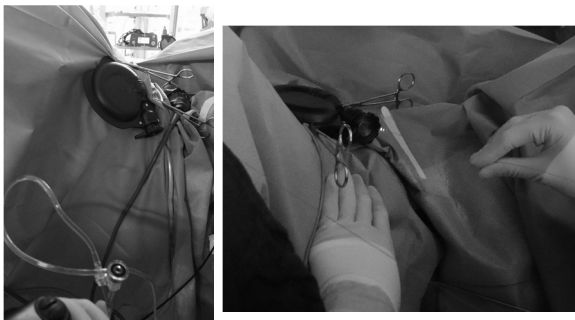
Securing the laser fiber - Laserdock

- Single use, disposable
- Accommodates fibers up to 2.3 mm in diameter
- Attach to drape with snaps



Printed with permission by Dr. Allen Seftel

Securing the laser fiber



Printed with permission by Dr. Allen Seftel

Safe Work Practices

- Operate class 3B and 4 lasers only in an area designed for laser operation and be certain that the beam is terminated on a diffuse beam block at the end of its use path.
- Do not enter a designated Class 3B or Class 4 laser controlled area (posted with a DANGER sign) without approval from a qualified laser operator.
- Always wear laser safety eyewear if a class 3B or class 4 invisible beam is accessible.
- Remove keys from lasers when not in use if necessary to prevent unauthorized laser operation.

Laser-Professionals.com

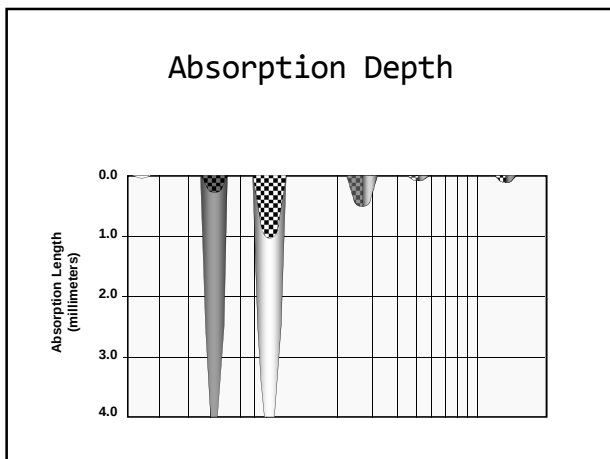
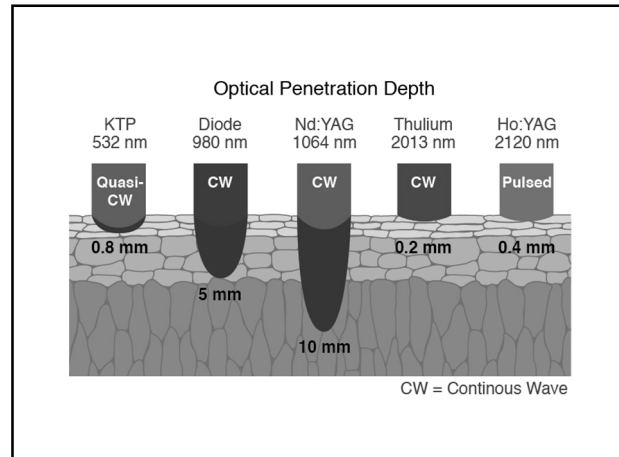
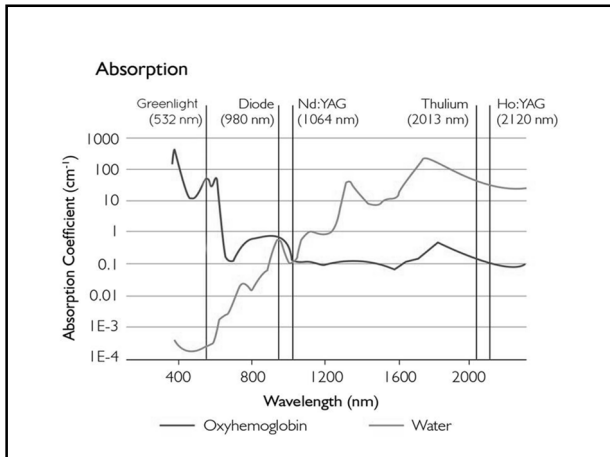
General Standard Operating Procedure

- ✧ Verify correct eyewear is available, and used as necessary.
- ✧ Uncover and/or post Laser Warning signs.
- ✧ Place at least one set of eyewear outside the NHZ.
- ✧ Turn on "Laser in Use" sign, if available.
- ✧ Close the door and cover windows, when applicable.
- ✧ Start and verify proper laser operations.
- ✧ Perform laser operations.
- ✧ When finished, turn off "Laser in Use" sign, cover/remove laser warning signs, remove keys and store keys in a secure location, if unauthorized laser use is likely.

Laser-Professionals.com

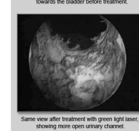
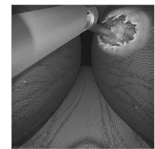
Most commonly utilized urologic lasers

- KTP (Greenlight, PVP)
- Holmium
- Diode (Biolitec, Evolve)
- Thulium (Revolix)
- CO₂
- Nd:Yag (in the past used often, making a comeback now for upper tract disease)

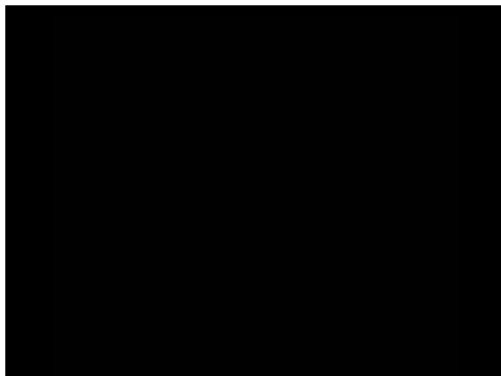


KTP Potassium titanyl phosphate

- 532 nm wavelength
- Visible (Green)
- Absorbed by hemoglobin
- Low absorption by water
- Side fire laser
- Optical penetration 0.8mm
- Coagulation depth 1-2mm



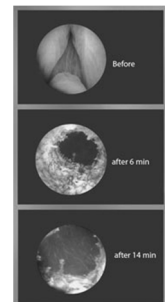
PVP



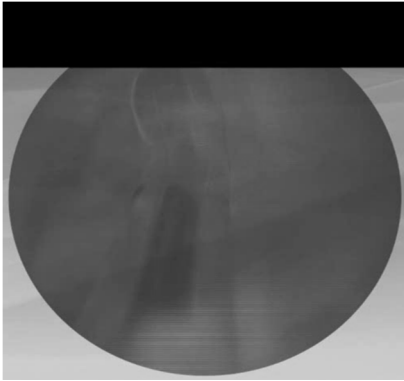
With permission of American Medical Systems

Diode

- 980, 1083, 1318 nm wavelengths
- Semiconductor
- Absorbed by water and hemoglobin
- 5.0 mm penetration
- 180 watt unit
- Contact fiber, "Twister", "Excavator"



Diode



With permission by Biolitec

Diode 810 nm – Hair Removal



With permission of Lumenis

Thulium

- Diode pumped solid state laser (DPSS)
- Absorbed by water
- 2013 nm wavelength
- Continuous energy
- 0.4 mm penetration
- Revolix 50W, 70W, 120W, 200W
- Revolix Junior 15W, 30W

Thulium



With permission of Lisa Laser

Thulium Prostate



With permission of Lisa Laser

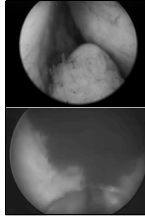
Thulium - Kidney



With permission of Lisa Laser

Holmium:YAG

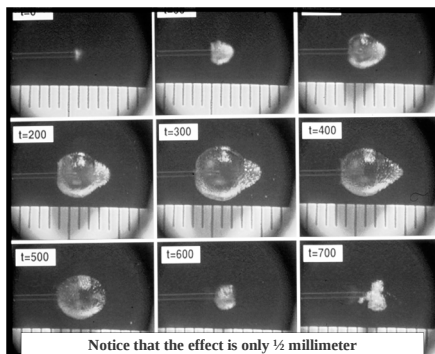
- 2140 nm wavelength
- High absorption in water
- Penetration <0.5mm
- Energy released in a pulsed fashion
- Side or end fire fibers



Moses Effect

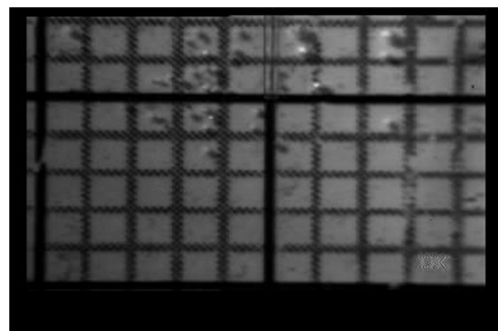
Because Holmium laser energy is well-absorbed in water, when it is released in a water-filled environment (like endourology) it actually creates a vapor bubble in the water. This is known as the "Moses Affect" since the water is parted by the bubble that forms.

Moses Effect



With permission of Lumenis

Moses Effect



With permission of Lumenis

HoLAP



HoLEP

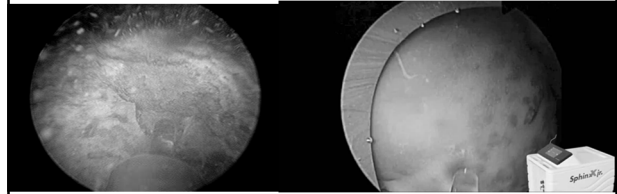


With permission of Dr Lori Lerner

Holmium for Stones

- Turbulence comes from energy, much less from frequency
- Holmium is pulsed, so higher freq leads to less “pulse” effect
- 20 watt lasers have much less efficacy
- Dusting
 - High frequency (50-70 Hz)
 - Low energy (0.2-0.4 joules)
- Fragmentation
 - Lower frequency (10 Hz)
 - Higher energy (0.8-1.0 joules)

Stone Dusting and Fragmenting



0.2 J and 50 Hz

3.0 J and 10 Hz

With permission of Lumenis and Lisa Laser

CO2 Lasers

- 10600 nm wavelength
- 15 and 25 watt systems
- Absorbed by water
- Very shallow penetration at 0.1 mm
- Continuous wave, pulse, and super pulse operation modes
- Depth controlled by watt level
- Coagulation range controlled by pulse duration



CO2 Lasers

- Articulating arm with end fire energy delivery
- Used for skin lesions, such as genital warts
- Now being applied to vaginal tissue
- Skin resurfacing
- Can seal blood vessels less than 0.5 mm
 - Reportedly less bleeding, edema, improved post op healing

CO2 - Incision



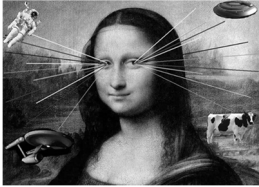
Case footage courtesy of:
George Lawson, MD - Marc Remacle, MD

CO2 - Facial Resurfacing



<https://www.youtube.com/watch?v=0Lt2uBzNoLM>

Vaginal Rejuvenation



Indications for Application of Vaginal Laser Therapy

- Genitourinary syndrome of menopause (vaginal atrophy associated with lack of estrogen)
- Lichen Sclerosis
- Vulvodynia/Vestibulitis
- ** Stress Incontinence
- ** Recurrent UTI's

Available Energy Sources

- Fractional Laser Systems
 - CO₂ Lasers
 - Femilift – Alma
 - FemTouch – Lumenis
 - MonaLisa Touch – DEKA/Cynosure
 - FDA approval for incision, excision, ablation, vaporization, and coagulation of soft tissue in gynecology
 - Erbium YAG Lasers
- RFA
 - Requires needles

Courtesy of Mickey Karram, MD

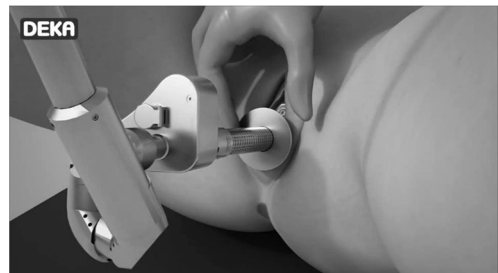
Erbium YAG

- Intimalase® – Fotona (not in USA)
- Incontilase® - Fotona (not in USA)
- Three treatments 30 days apart
- Strongly absorbed by water
- Has been studied for use for SUI and Genitourinary syndrome of menopause (vaginal atrophy associated with lack of estrogen)

Vaginal Resurfacing

- Genitourinary syndrome of menopause
 - Fractional resurfacing
 - The entire surface area is not treated, reportedly improving wound healing due to existing surrounding tissue
 - Creates inflammatory reaction → fibroblasts released → new collagen formation, improved vascularity, transudate improves dryness, vagina becomes more acidic, increased lactobacilli and glycogen

Vaginal resurfacing



<https://www.youtube.com/watch?v=yP5wpoiieuU>

Conclusions

- Laser energies have properties that make them ideal tools for use in urologic surgeries and diseases
- Laser wavelengths are unique and the properties of one are not applicable to another
- Risks vary based on wavelength and it is imperative that users understand and appreciate the differences
- Above all, do no harm. Educate and inform yourself.

Neurogenic Bladder: Recurrent Urinary Tract Infections – Beyond Antibiotics

Comprehensive Review of Urology
September 21, 2018

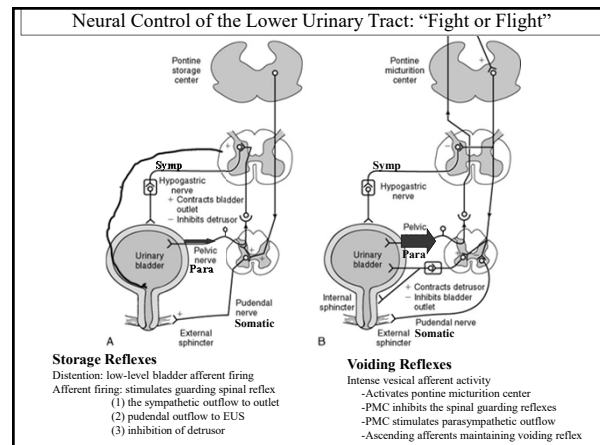
Elise J.B. De, MD
Massachusetts General Hospital

Disclosures

Reports no relationships with a commercial interest

Objectives

- Approach to UTI in Neurogenic Bladder
- Role of Emptying, Pressures, Foreign Bodies
- Secondary workup and Intervention



History

- Intake forms
- Voiding diaries
- Active questioning:
 - Prior surgeries
 - Bowel function
 - Pelvic organ prolapse
 - Neurological disease
 - Adherence to routine health screening: PSA, Colonoscopy
 - Bladder management prior to NGB
 - Bladder management since NGB
 - Independence, Technique

Elevated Storage Pressures

- Elevated bladder storage pressures from poor bladder compliance or detrusor over activity can lead to vesicoureteral reflux, impaired peristalsis of the ureters, hydronephrosis, and a theoretical risk of bacteria traversing epithelial barriers into the bladder.
 - Anticholinergics
 - Botulinum toxin
 - Continuous Drainage

Role of the Bladder

Storage



Facilitated by:
-Anticholinergics
-Augment
-Botulinum Toxin

Emptying



Facilitated by:
-Intermittent Cath
-Outlet procedures
-Diversion
-Indwelling Cath
-Alpha Blockers

Voiding / Complete Emptying

- Voiding to completion/ emptying is a protective mechanism against UTI.
 - One animal study showing that 99.9% of bacteria injected into the bladder are eliminated by voiding
 - The higher the postvoid residual volume (PVR) the higher the risk of UTI has been found

Norden CW, Green GM, Kass EH. Antibacterial mechanisms of the urinary bladder. J Clin Invest. 1968 Dec;47(12):2689-700.
Kim BR, Lim JH, Lee SA, Kim JH, Koh SE, Lee IS, Jung H, Lee J. The Relation between Postvoid Residual and Occurrence of Urinary Tract Infection after Stroke in Rehabilitation Unit. Ann Rehabil Med. 2012 Apr;36(2):248-53.

Method of Emptying

- Patients with neurogenic bladder often require indwelling catheters or CIC
- In a retrospective study evaluating patients with neurogenic bladder, the emptying method was the most important predictor of symptomatic UTIs
- Indwelling catheterization posed the highest risk¹⁰

Krebs J, Wöllner J, Pannek J. Risk factors for symptomatic urinary tract infections in individuals with chronic neurogenic lower urinary tract dysfunction. Spinal Cord. 2016 Sep;54(9):682-6.

PVR

Ultrasound - 51798
Catheterization - 51701

Storage



Emptying



Diagnosis of UTI

- Nuanced in this population
- Impaired bladder sensation
- Do not report classic symptoms.
- Intermittent catheterization or indwelling catheters for bladder emptying
 - Associated with increased rates of bacteriuria

True Infections

1st Line

- Upper urinary tract imaging
- Cystoscopy
- Urodynamics/ Post-void residual
- Patients who self-catheterize: review of technique emptying
- Indwelling Cath: Management Strategy

2nd Line

- Cystogram/VCUG: Fistula, Reflux
- MRI: Urethral diverticulum

Coexisting Diagnoses

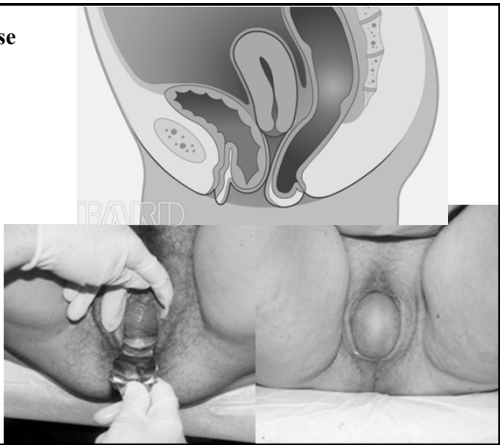
Atrophic Vaginitis



Estrogen
Vulvar Irritants

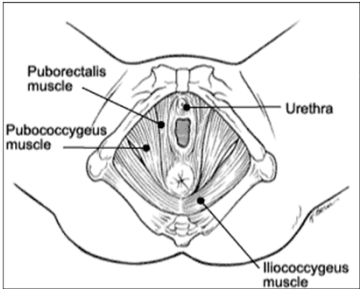
Am Fam Physician. 2000 May 15;61(10):3090-6 **Diagnosis and treatment of atrophic vaginitis.**
Bachmann GA, Nevadunsky NS.

Prolapse



Pelvic Floor Dystonia

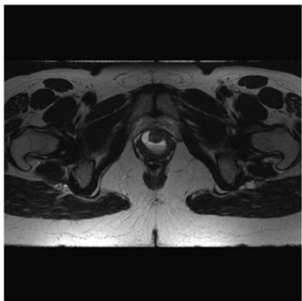
Essential Part of the Physical Exam
Cross-talk along the S2,3,4 Pathways



© 2001 Kohnen Born

Coexisting Diagnoses

UTI/Fistula



Coexisting Diagnoses

Infection with Variable Cultures

- Possible urethral irritation (Estrogen, Toilet Paper, Soap)
- Men: expressed prostatic secretions
- Women: vaginal swab for ureaplasma and mycoplasma
- Symptoms of UTI can derive from pelvic floor muscle spasm
 - Cross – sensitization along S 2,3,4 nerve pathways [Malykhina 2007]
- If “UTI” symptoms persist, workup obligatory:
 - Carcinoma in situ
 - Bladder stones
 - Urethral diverticulum

Imaging

- Renal ultrasound suffices for recurrent UTI
- Renal mass protocol CT scan or MRI should be performed instead in the case of hematuria
 - ≥ 3 red blood cells per 40x high power microscopic view on urine sediment in the absence of infection or clearly documented genitourinary trauma

Stones



- Urinary stasis as well as infection can cause urinary calculi, which in turn may act as nidi for infection.
- Obstructing or large stones should be removed. Non-obstructing small upper urinary tract stones are usually thought to be benign.
- There is some evidence that removal of nonobstructing asymptomatic renal calculi in those with recurrent UTIs can resolve infections in 50%

Zanetti G, Paparella S, Trinchieri A, Prezioso D, Rocco F, Naber KG. Infections and urolithiasis: current clinical evidence in prophylaxis and antibiotic therapy. Arch Ital Urol Androl. 2008 Mar;80(1):5-12.
 Omar M, Abdulwahab-Ahmed A, Chaparala H, Monga M. Does Stone Removal Help Patients with Recurrent Urinary Tract Infections? J Urol. 2015 Oct;194(4):997-1001.
www.kidneystones.org, <http://urologystone.com/CH06DiagnosisOfStones/helical.html>

Constipation

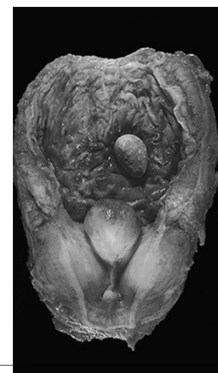
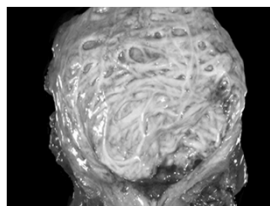
- Constipation and fecal incontinence are both thought to increase the propensity toward urinary tract infection.
- Mechanisms include perineal contamination, combined bladder and defecatory dysfunction via neural crosstalk, and trans colonic migration of bacteria.
- Intervention to address constipation or incontinence should be encouraged as part of the treatment plan for the UTI

Obstruction

- Renal obstruction can occur at the level of the ureteropelvic junction (UPJ), any segment of the ureter, or ureterovesicular junction (UVJ) secondary to urolithiasis, scarring, or congenital abnormalities (e.g. valves or crossing vessels).
- The bladder is often a source of obstruction due to elevated pressures, detrusor sphincter dyssynergia, pre-existing prostatic obstruction, or anterior vaginal wall prolapse.
- Obstruction anywhere in the urinary tract needs to be addressed to prevent loss of renal function, decompensation of the obstructed unit (e.g. bladder), and prevention of infection.

BOO

Damage to nerves, synapses and smooth muscle cells due to initial poor blood flow followed by generation of reactive oxygen and nitrogen species during reperfusion [Mannikarottu 2005].



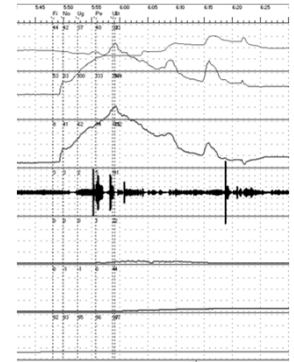
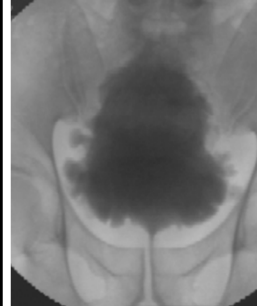
Treat BOO and OAB

Beware the Condom Cath

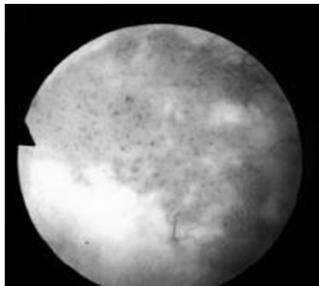


Coexisting Diagnoses

DO and BOO



Cystoscopy seeking stones, foreign body, obstructing prostate or fistula, stricture fistula, tumor, or urethral diverticulum should be performed



Urodynamics

- Should be performed in most patients with recurrent UTI in the setting of spinal cord injury
- Patients with stroke, Parkinson's disease, and multiple sclerosis who have bladder dysfunction and/or recurrent UTI

Urodynamics

Rectal Balloon Catheter



Dual Lumen Urethral Catheter

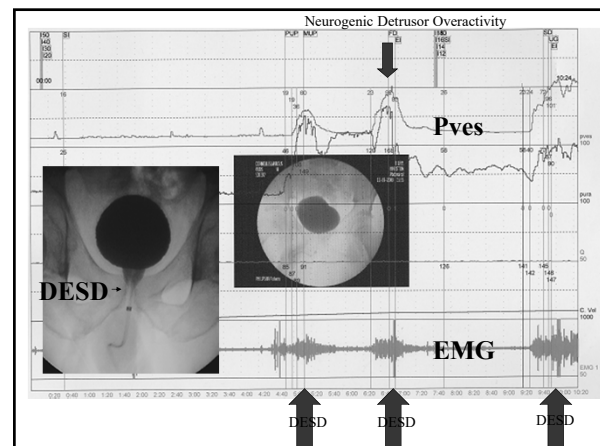
CAT208

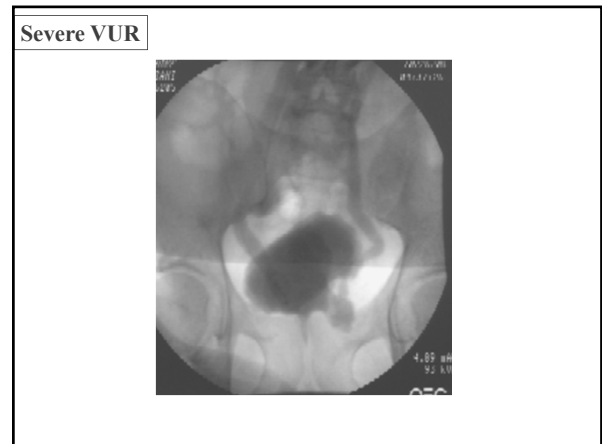
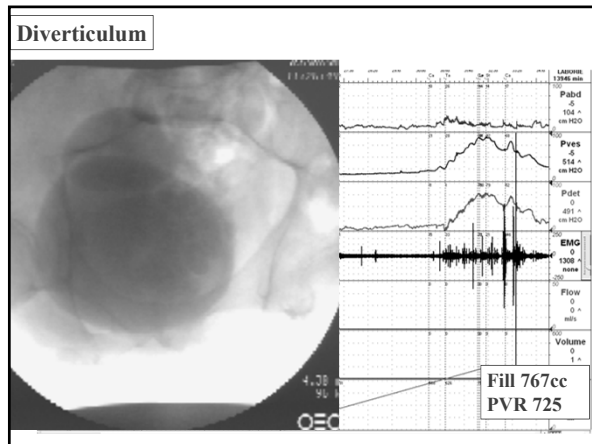


EMG



Tower





UTI Management

- Symptoms of:
 - Frequency
 - Urgency
 - Burning with urination
- Cloudy or Bloody Urine
- Odor
- Spasticity
- Fatigue
- Altered Mental Status

Bacteria in NGB

- The microbiome of patients with neuropathic bladder is intrinsically different from those with normal functioning bladders.
- *Lactobacillus* is the prevalent species in healthy women and *Corynebacterium* in men
- *Enterobacteriaceae* species, which includes *E. coli* and *Klebsiella*, is the most prevalent in neurogenic bladder^{15,16}.
- Patients in the hospital are more likely to have *Pseudomonas*, *Acinetobacter*, and *Enterococcus* species with extensive resistance patterns. These data warrant avoidance of treating urinary infections until the susceptibilities of the target organism are known.

Fouts DE, Pieper R, Szpakowski S, et al. Integrated next-generation sequencing of 16S rDNA and metaproteomics differentiate the healthy urine microbiome from asymptomatic bacteriuria in neuropathic bladder associated with spinal cord injury. *Journal of Translational Medicine*. 2012;10:174.
 Levy J, Breton F, L., Jousse M., Haddad R., Verollet D., Guinet-Lacoste A., & Amarengo G. Bacterial ecology and antibiotic resistance in patients with neurogenic overactive bladder treated by botulinum toxin injections. *Annals of Physical and Rehabilitation Medicine*. 2013 56.
 Hayano Y, Takahashi S, Uehara T, Hashimoto J, Nishimura K., Kitamura H., & Masumori N. Emergence of antimicrobial-resistant uropathogens isolated from pediatric patients with cystitis on daily clean intermittent catheterization. *Journal of Infection and Chemotherapy*. 2015; 21(10): 703-706.

Duration of Antibiotics

- Guidelines recommend a 7 day course for those who have prompt resolution of symptoms.
- If delayed response, 10-14 days is appropriate course.
- Indwelling catheters should be exchanged in the setting of infection to obtain the specimen off the new catheter and to improve the likelihood of successful treatment
- In difficult cases, consider changing the indwelling catheter a second time once on appropriate antibiotics.

Hooton T et al: Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America, *Clinical Infectious Diseases*, Volume 50, Issue 5, 1 March 2010, Pages 625-663

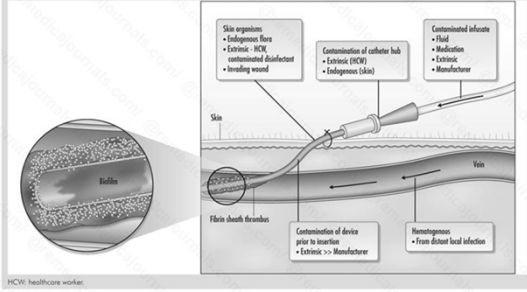
Antibiotic Prophylaxis

- Systemic antimicrobial prophylaxis should not be used for those with neurogenic bladder and recurrent UTIs.
- Several studies have examined the use of nitrofurantoin, fluoroquinolones, and trimethoprim/sulfamethoxazole as prophylaxis
- A Cochrane review concluded the benefits of antibiotic prophylaxis do not clearly outweigh the adverse effects such as antimicrobial resistance

Niël-Weise, B. S., & Broek, P. J. (2005). Urinary catheter policies for long-term bladder drainage. *Cochrane Database of Systematic Reviews*.

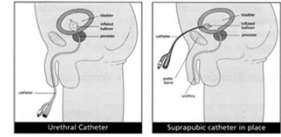
Tubes Biofilm

Figure 2. Diagram of an intravenous catheter with biofilm growth.



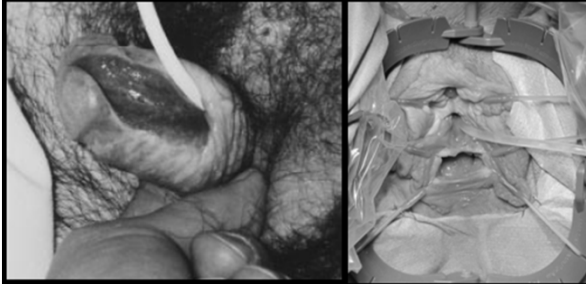
UTI With Indwelling Catheter

- Culture off new catheter
- Cloudy
- Odor
- New leakage
- Autonomic dysreflexia
- Pain
- Fever
- Mental Status Change



Iatrogenic Hypospadias

- Keep Foley Off Tension
- Short – term urethral catheterisation
- CIC or Suprapubic Tube



Catheter Associated UTI

- All UTIs in neurogenic bladder patients are considered “complex”.
- In accordance with IDSA Guidelines, catheter-associated UTIs, which include indwelling and intermittent catheterization, are defined as the presence of clinical symptoms along with $>10^3$ colony-forming units/mL of one or more bacterial species obtained from a clean catheterized specimen¹⁸.
- For those with indwelling catheters or suprapubic tube, the specimen should be obtained from the new tube after the catheter has been exchanged.
- Changing the catheter will improve the accuracy of identifying a culprit organism and also may improve the response to antibiotic therapy by removing the biofilm that serves as a scaffold for reinfection

Hooton T et al: Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America, Clinical Infectious Diseases, Volume 50, Issue 5, 1 March 2010, Pages 625–663
Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. American journal of infection control. 2004;32(3):177-183.

Suprapubic Catheter

- Suprapubic catheter often becomes the management of choice for neurogenic bladder. This method is favored due to low-impact placement, reduced UTI risk and urethral complications versus urethral catheter, reversibility, and convenience for patients who cannot catheterize themselves. The use of antibiotics during the exchange did not alter the incidence of infection⁵²; thus, the use of antibiotics at the time of catheter change is not recommended.
- Consider changing the catheters monthly, or earlier if indicated (clogging, symptomatic infection), as this allows for elective changes and avoidance of morbidity.
- Lastly, catheters used for suprapubic drainage should be larger bore (18-22 French), flexible for comfort, and short-tipped to prevent erosion of the bladder surface.

Sorokin, Igor, and Elise De. “Options for Independent Bladder Management in Patients with Spinal Cord Injury and Hand Function Prohibiting Intermittent Catheterization.” *Neurourology and Urodynamics*, vol. 34, no. 2, 2013, pp. 167–176., doi:10.1002/nau.22516.

Biofilm

- There are two routes of biofilm development on indwelling catheters: intraluminal and extraluminal. Intraluminal biofilm formation occurs when organisms gain access to the internal lumen of the catheter through failure of the closed drainage system or contamination of the collection bag.
- A closed-catheter drainage system should be used to reduce urinary infections.
- There is inadequate evidence to recommend single-use or daily change of urinary leg drainage bags to reduce UTIs⁵⁹; consider a leg bag changing interval between 5 days up to 1 month
- Randomized controlled trials to establish the optimum time interval between changing drainage bags are needed.

Cottenden, A. et al. Management Using continence products (2017). Incontinence (6th ed.). Bristol, UK: International Continence Society.
Ostaszewicz J, Paterson J. Nurses' advice regarding sterile or clean urinary drainage bags for individuals with a long-term indwelling urinary catheter. J Wound Ostomy Continence Nurs. 2012 Jan-Feb;39(1):77-83.

Antimicrobial Coatings

- Long-term catheterization (>30 days) was assessed in a Cochrane review of randomized trials, but the authors were unable to report a definitive conclusion due to inadequate evidence⁶⁸

Jahn P, Preuss M, Kernig A, et al. Types of indwelling urinary catheters for long-term bladder drainage in adults. Cochrane Database Syst Rev. 2007pg. CD004997.

Irrigation

- Antibiotic Irrigations - conflicting data to support this technique. Individual clinicians do employ irrigation strategies with select patients. Examples include Gentamycin, Neomycin, and simply saline.
- Meta-analysis of intravesical aminoglycoside treatment :conflicting data.
- Review of seven retrospective European studies suggests irrigation with hyaluronic acid and chondroitin sulphate decrease the frequency of UTIs (restoring the glycosaminoglycan bladder layer).
- Guidelines recommend against the use catheter irrigation with antimicrobial agents due to conflicting data.

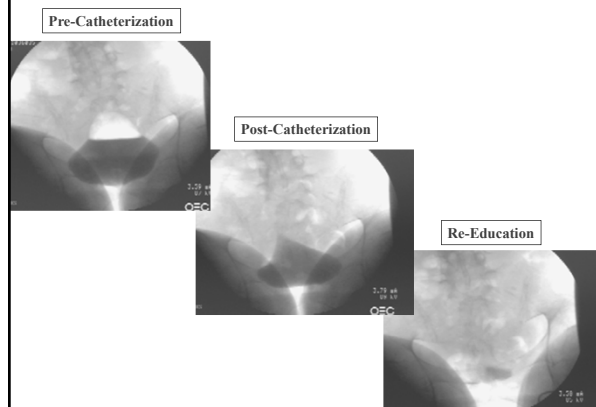
Van Nieuwkoop C, Den Exter PL, Elzevier HW, Den Hartigh J, Van Dissel JT. Intravesical gentamicin for recurrent urinary tract infection in patients with intermittent bladder catheterisation. International Journal of Antimicrobial Agents. 2010; 36 (6): 485-90.
National Clinical Guideline Centre (NICE) (UK). Infection: Prevention and Control of Healthcare-Associated Infections in Primary and Community Care: Partial Update of NICE Clinical Guideline 2. London: Royal College of Physicians (UK); 2012 Mar. (NICE Clinical Guidelines, No. 139.) 10. Long term urinary catheters. <https://www.ncbi.nlm.nih.gov/books/NBK115272/>
Ciccone A, Cattiello F, Ucciero G, et al. Intravesical treatment with highly-concentrated hyaluronic acid and chondroitin sulphate in patients with recurrent urinary tract infections: Results from a multicentre survey. Canadian Urological Association Journal. 2014;8(9-10):E721-E727.

Intermittent Catheters

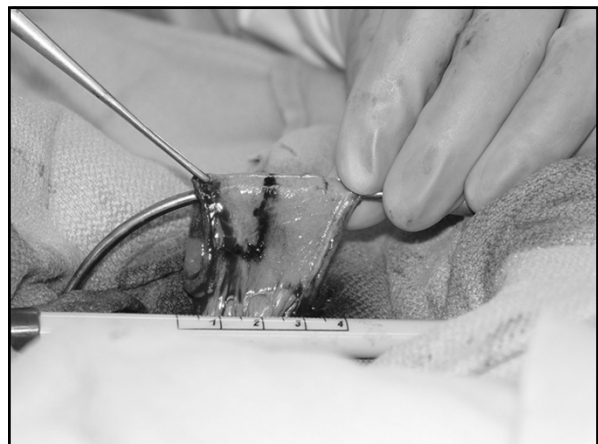
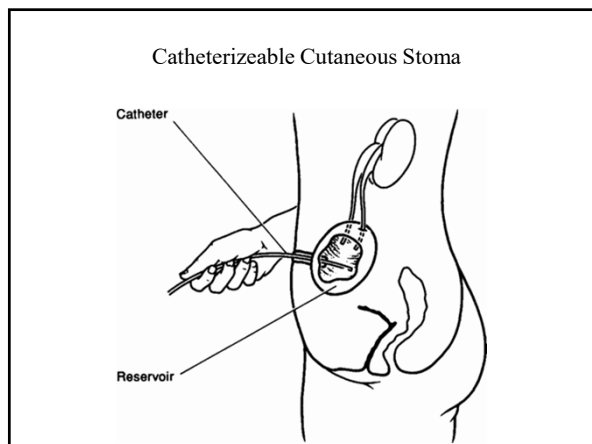
- Several intermittent catheter techniques have been evaluated for risk of UTI
- The largest Cochrane review and meta-analysis found no superior method to prevent UTIs.
- The cost of catheters, limited third-party insurance reimbursement, and increased environmental waste are issues associated with single use, sterile catheters.
- The Cochrane conclusions are to allow patient preference to guide management.
- Traditionally catheters with a siliconized or polyvinyl chloride, non-pretubricated, non-hydrophilic surface have been rewashed without evidence of inferiority.
- For patients who rewash catheters, the authors recommend changing to a new catheter every week, washing with water and clear-rinsing dish soap, then drying the catheter in open air.
- Alternatively, for convenience some patients use reusable catheters at home and single use catheters while out.

Bermingham SL, Hodgkinson S, Wright S, Hayter E, Spinks J, Pellowe

Coexisting Diagnoses: UTI

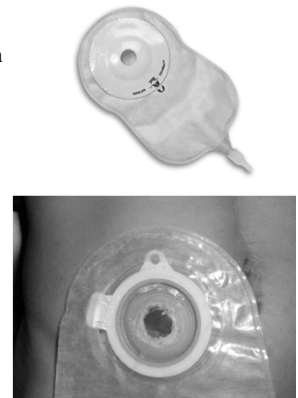
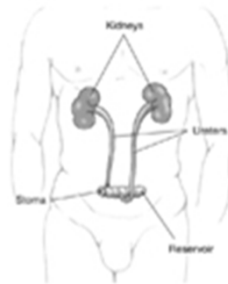


Catheterizable Cutaneous Stoma





Alternatives – Ileal Loop Urinary Diversion



Proanthocyanidins “Cranberry”

- There is conflicting literature regarding cranberry supplements, in part due to the significant heterogeneity and lack of standardization of the supplements as well as the clinical outcomes evaluated (i.e., complicated or recurrent UTIs)

Mody L, Juthani-Mehta M. Urinary Tract Infections in Older Women: A Clinical Review. JAMA. 2014;311(8):844-854.
Liska DJ, Kern HJ, Maki KC. Cranberries and Urinary Tract Infections: How Can the Same Evidence Lead to Conflicting Advice? Adv Nutr. 2016 May 16;7(3):498-506

Probiotics

- A 2015 Cochrane Review examined 9 quasi-randomized controlled trials and randomized controlled trials evaluating the use of probiotics, predominantly *Lactobacillus* species. They concluded that there was no significant benefit demonstrated for probiotics, but because there was insufficient data, a benefit could not be ruled out ⁹¹

Schwenger EM, Tejani AM, Loewen PS. Probiotics for preventing urinary tract infections in adults and children. Cochrane Database Syst Rev. 2015 Dec 23;(12):CD008772

Other Orals

- Ascorbic acid - alkalization of urine – conflicting data
- Methenamine salts convert to formaldehyde in acidic urine, which then exhibits nonspecific antiseptic activity that is dependent on dwell
- D-mannose inhibiting bacterial adherence to urothelial cells by blocking Type 1 fimbriae

Vaccines/ Immunostimulants

- **OM-89** - oral immunostimulant - 18 different serotypes of heat-killed uropathogenic *E. Coli*, thought to decrease recurrent UTIs by stimulating innate immunity
- **Vaginal vaccine** available in Europe, is a vaccine incorporating 10 heat-killed uropathogenic *E. Coli*, *Proteus vulgaris*, *Klebsiella pneumonia*, *Morganella morganii*, and *Enterococcus faecalis*,
- **Intranasal vaccine** based on adhesin proteins in uropathogenic *E. coli* and *P. mirbalis*

Wagenlehner FM, Ballarini S, Pilatz A, Weidner W, Lehr L, Naber KG. A Randomized, Double-Blind, Parallel-Group, Multicenter Clinical Study of Escherichia coli-Lyophilized Lysate for the Prophylaxis of Recurrent Uncomplicated Urinary Tract Infections. *Urol Int*. 2015;95(2):167-76.
Uehling DT, Hopkins WJ, Elkahwaji JE, Schmidt DM, Levenson GE. Phase 2 clinical trial of a vaginal mucosal vaccine for urinary tract infections. *J Urol*. 2003 Sep;170(3):867-9.
Habibi M, Asadi Karam MR, Shokgozar MA, Oloomi M, Jafari A, Bouzari S. Intranasal immunization with fusion protein MrpH-FimH and MPL adjuvant confers protection against urinary tract infections caused by uropathogenic Escherichia coli and Proteus mirabilis. *Mol Immunol*. 2015 Apr;64(2):285-94.

Conclusion

- The improvement in care for persons with neurogenic bladder over the last several decades has improved renal morbidity, mortality, and overall quality of life.
- A combination approach including management of anatomic and functional factors with careful medical intervention can significantly improve frequency of urinary infection.
- Further study of non-antibiotic therapeutic strategies are much needed as we recognize the complexity of the urinary biomes and the limitations of antibiotic therapies.

**PREVENTING HEALTHCARE-ACQUIRED
CATHETER-ASSOCIATED URINARY TRACT INFECTIONS**

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University of Michigan, Ann Arbor
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Funding/Support provided by the NIA, CDC,
AHRQ and non-profit foundations

OUTLINE

- Strategies to preventing Catheter-associated UTI (CAUTI) in:
 - Hospitalized patients
 - Post-acute and long-term care patients
- Non-infectious complications of indwelling urinary catheters
- Appropriate indwelling urinary catheter use in peri-operative period

**INDWELLING URINARY CATHETER USE IN HOSPITALS AND
SKILLED NURSING FACILITIES**

- Hospitalized patients
 - 5, 534 hospitals in US with 900K admissions/yr.
 - ~ 30% (ICU > non-ICU) with indwelling urinary catheters
 - 1 to 1.5 million catheter-days/yr.
- Skilled nursing facility patients
 - 15, 200 facilities with 1.4 million individuals any given day
 - 5% with indwelling urinary catheters (~ 70,000)
 - average 100 days/catheterized resident
 - 7 million catheter-days/yr.

The **NEW ENGLAND**
JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2016 VOL. 374 NO. 22

**A Program to Prevent Catheter-Associated Urinary Tract
Infection in Acute Care**

Sanjay Saint, M.D., M.P.H., M. Todd Greene, Ph.D., M.P.H., Sarah L. Krein, Ph.D., R.N., Mary A.M. Rogers, Ph.D.,
David Ratz, M.S., Karen E. Fowler, M.P.H., Barbara S. Edson, R.N., M.B.A., M.H.A.,
Sam R. Watson, M.S.A., C.P.P.S., Barbara Meyer-Lucas, M.D., M.H.S.A., Marie Masuga, R.N., M.S.N.,
Kelly Faulkner, M.S.P.A., Carolyn V. Gould, M.D., M.S.C.R., James Battles, Ph.D.,
and Mohamad G. Fakih, M.D., M.P.H.

Table 1. Program Recommendations and Examples of Interventions.*	
Recommendation	Example of Intervention
Primary	
Conducting daily assessment of the presence of and need for an indwelling urinary catheter	Conducting daily nursing rounds to review urine-collection strategies, including indications for continued urinary-catheter use
Avoiding use of an indwelling urinary catheter by considering alternative urine-collection methods	Promoting the use of condom catheters, bladder scanners, intermittent straight catheterization, and accurate measurement of daily weight (all in lieu of indwelling urinary catheters)
Emphasizing the importance of aseptic technique during catheter insertion and proper maintenance after insertion	Developing or updating the catheter-insertion policy to include all the proper steps, developing competencies for health-care workers who insert catheters, and considering periodic audits of catheter placement
Additional	
Providing feedback to the units regarding urinary-catheter use and catheter-associated UTI rates	Providing nurses and physicians with data on urinary-catheter use, with monthly feedback on use and catheter-associated UTIs
Addressing any identified gaps in knowledge of urinary-management processes†	Conducting an evaluation for gaps in knowledge of infectious and noninfectious consequences of urinary-catheter use; developing tailored educational materials to fill identified gaps; using multiple venues for education, including bedside and electronic; incorporating education into annual competency testing for nurses; and using multiple venues for physicians (formal presentations and meetings, with one-to-one discussions for physicians with high use)

* UTI denotes urinary tract infection.
† Urinary management processes include proper insertion and maintenance of indwelling urinary catheters, use of alternative urine-collection methods, and prevention of infectious and noninfectious consequences of urinary-catheter use.

WHAT'S IN THE TOOLKIT (TIERS) FOR REDUCING INDWELLING URINARY CATHETER USE?

TECHNICAL strategies: can be solved with existing science (knowledge) or technology

Technological fixes to make urinary collection/measure **easy** without indwelling catheters

Knowledge/Guidelines to inform decisions to place/remove urinary catheters:

SOCIO-ADAPTIVE strategies: require a change in beliefs, attitudes, or values.

Behavior-based strategies:

- Team-based approach
- Leadership of the problem
- Bedside nurse champion
- Bedside physician champion
- Accountability of IUC use rates
- Actionable feedback
- Ensure sustainability

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- Bedside physician champion
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- Actionable feedback
- Ensure sustainability

Guidelines alone do not change catheter use. People do.

Table 3. Multivariable-Regression Estimates of Changes in Catheter-Associated UTI Rates, According to Unit Type.^a

Variable	Non-ICU (N=553)		ICU (N=373)	
	IRR (95% CI)	P Value	IRR (95% CI)	P Value
Time†‡	0.68 (0.56-0.82)	<0.001	1.01 (0.87-1.17)	0.90
Teaching hospital	1.76 (1.03-3.01)	0.04	1.92 (1.32-2.80)	0.001
Rural hospital	0.90 (0.66-1.23)	0.51	0.83 (0.58-1.18)	0.30
Critical-access hospital	2.36 (1.65-3.37)	<0.001	2.60 (0.94-7.20)	0.07
Hospital size (per 100-bed increase)§	0.97 (0.90-1.05)	0.45	1.09 (1.02-1.16)	0.01

^a Incidence rate ratios (IRRs) are shown for changes from baseline in the rates of catheter-associated UTI. On the basis of the definition used by the Centers for Disease Control and Prevention's National Healthcare Safety Network, the catheter-associated UTI rate was calculated as the number of urinary tract infections per 1000 catheter-days. Negative binomial models were fit, with random intercepts for hospital and unit. CI denotes confidence interval.

† Time was defined as the number of days from the end of the baseline period (day 0) to the end of the sustainability period (day 427). Thus, the IRR indicates the percentage change from the end of baseline to the end of the study period.

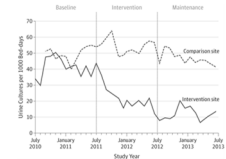
‡ P=0.001 for the comparison between non-ICUs and ICUs.

§ P=0.001 for the comparison between non-ICUs and ICUs.

CAUTI PREVENTION

Dissemination, audit & feedback:

- Streamlined diagnostic algorithm CAUTI vs. asymptomatic bacteriuria
- Interactive case-based audit and feedback
- 2 VA healthcare systems and NHs



Trautner BW et al. JAMA Intern Med 2015;175:1120-7

JAMA Internal Medicine | Original Investigation

A Multicenter Study of Patient-Reported Infectious and Noninfectious Complications Associated With Indwelling Urethral Catheters

Sanjay Saint, MD, MPH; Barbara W. Trautner, MD, PhD; Karen E. Fowler, MPH; John Coluzzi, BA; David Ratz, MS; Erica Lencucha, MD; John M. Hollingsworth, MD, MS; Sarah L. Kneis, PhD, RN

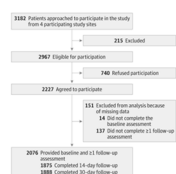
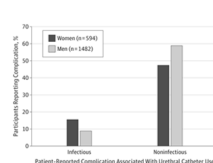


Table 1. Demographic and Baseline Characteristics of 2076 Study Participants

Characteristic	No. (%)
Age, mean (SD), y	60.3 (11.4)
Sex	
Male	1462 (70.4)
Female	594 (28.6)
Race/ethnicity	
White	1653 (79.6)
African American	290 (14.0)
American Indian or Alaska Native	27 (1.3)
Other or unknown ^a	106 (5.1)
Reason for urethral catheter placement	
Postoperative or for surgical procedure	1653 (79.6)
Urinary incontinence or bladder obstruction	144 (6.9)
Acute or chronic renal insufficiency	50 (2.4)
Patient convenience or convenience	31 (1.5)
Research or surveillance	25 (1.2)
Other or unknown	103 (5.0)
Exposure to antibiotics, antifungals, or other drugs during urethral catheter insertion	144 (6.9)
Exposure to antibiotics, antifungals, or other drugs during urethral catheter maintenance	414 (20.0)
Exposure to antibiotics, antifungals, or other drugs during urethral catheter removal	144 (6.9)
Number of days catheter was in place	1378 (66.0)



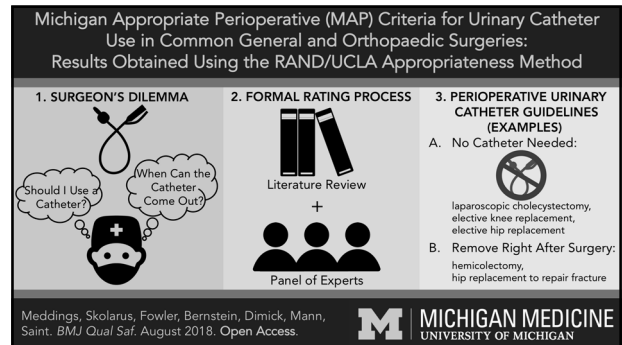
JAMA Network

MICHIGAN APPROPRIATE PERIOPERATIVE (MAP) CRITERIA FOR URINARY CATHETER USE

- Used the RAND/UCLA Appropriateness Method to assess the appropriateness of urinary catheter placement and timing of removal for common adult general and orthopedic surgeries
 - Review of existing literature
 - Development of clinical scenarios
 - Expert panelists rated appropriateness 1st individually, then again in person after group discussion

RESULTS

- Appropriateness of catheter use varied by expected procedure time, expected intravenous fluids, and procedure-specific risks
- Summarized ratings into 3 groups:
 1. Can perform surgery without catheter
 2. Use intraoperatively only, ideally remove before leaving OR
 3. Use intraoperatively and keep catheter until post-op day 1 to 4



RECOMMENDATIONS FOR SAMPLE SURGERIES

Can Perform Surgery without Catheter

- Laparoscopic cholecystectomy
- Open appendectomy
- Unilateral elective total hip arthroplasty
- Unilateral total knee arthroplasty

Original Investigation

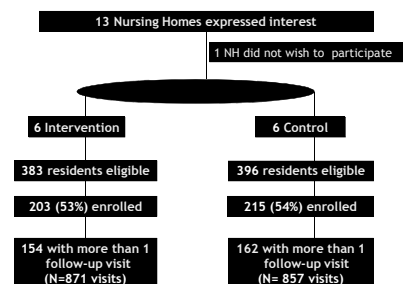
**A Targeted Infection Prevention Intervention
in Nursing Home Residents With Indwelling Devices
A Randomized Clinical Trial**

Lima-Mody, MD; Sarah L. Klein, PhD; Sanjay K. Saint, MD; Lilian C. Min, MD; Ana-Maria, MD; Bonnie Lansing, LPH; Sara E. McNamara, MPH; Kathleen Symons, BA; Jay Fisch, BS; Evonne Koo, MPH; Ruth Anne Rye, BS; Andrzej Galecki, MD, PhD; Mohammed U. Kabeta, MS; James T. Fitzgerald, PhD; Russell N. Olmsted, MPH; Carol A. Kaufman, MD; Suzanne F. Bradley, MD

Table 1. Overview of Targeted Intervention Process (PDP) Program Interventions		
	Intervention Group	Control Group (Shaded Cell)
Enrollment criteria (with or without screening)	Assignment based on randomization	Standard pre-assessment
Screening	Screening based on pre-assessment	Screening based on pre-assessment, as needed per protocol
Non-screened/eligible	Screening based on pre-assessment as needed per PDP strategy	Screening based on pre-assessment, as needed per protocol
Screening	Screening based on pre-assessment as needed per PDP strategy	Screening based on pre-assessment, as needed per protocol
Withholding resistant organs	Screening based on pre-assessment, as needed per PDP strategy	Screening based on pre-assessment, as needed per protocol
Infection	Screening based on pre-assessment, as needed per PDP strategy	Screening based on pre-assessment, as needed per protocol
Evaluation	Screening based on pre-assessment, as needed per PDP strategy	Screening based on pre-assessment, as needed per protocol
Not staff	Screening based on pre-assessment, as needed per PDP strategy	Screening based on pre-assessment, as needed per protocol

TARGETED INFECTION PREVENTION (TIP) STUDY

Design:	Cluster-randomized trial
Facilities:	12 NHs in SE MI
Population:	Residents with indwelling urinary catheters and/or feeding tubes
Duration:	2010-2013
Inclusion:	Device > 72 hrs., Informed consent
Exclusion:	Hospice care



RESIDENT PRECAUTIONS
This resident is taking part in a Research Study

Resident	Room

BEFORE ENTERING RESIDENT ROOM
Please wash your hands and wear gloves



WHEN PROVIDING DIRECT CARE
Please wear protective aprons



AFTER LEAVING RESIDENT ROOM
Please remove gloves and wash your hands



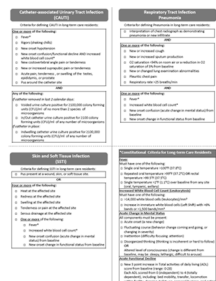
INFECTION PREVENTION IN AGING

FRONTLINE NURSING PERSONNEL



TIP Toolkit, page 15

PRESCRIBERS



How to define:

- UTIs
- Pneumonia
- Skin & Soft Tissue Infection

Distribution Strategy:

- Nurse
- Nurse Aide
- Physician
- Director of Nursing
- Administrator

TIP Toolkit, page 137

U of M TIP Research Study Report
ABC Medical Care Facility
Month 31 January 2013
Total 8 Residents Cultured 4

Figure 1. MDRO Colonization

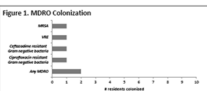


Table 1. New MDRO Acquisitions

MDRO	#
MRSA	2
ESBL	2
CRP	2

Table 2. New Infections

# Residents	Total # of Infections
1	1

Please follow Standard Barrier Precautions to reduce the # of residents colonized and help prevent further infections.

Please verify the TIP study team of any new eligible residents.

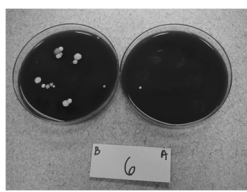
Thank you for your participation in the study!

LEADERSHIP

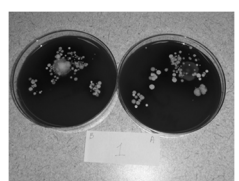
Monthly Report

- MDRO rates
- Infection rates
- Strategies

TIP Toolkit, page 16



GOOD TECHNIQUE



NOT-SO-GOOD TECHNIQUE

Mody L et al. JAMA Intern Med 2015; ICHE 2003

DIDACTIC



DEMONSTRATION



INFECTION CONTROL JEOPARDY





MEASURES

- Outcomes:
 - MDRO prevalence
 - Incident MDROs (new acquisitions)
 - Device-related urinary tract, upper respiratory tract infections
 - Clinical definitions

BASELINE CHARACTERISTICS

	Participants with ≥1 follow-up visit (2010-13)		
	Intervention (n=154)	Control (n=162)	P
Follow-up	116 days	104 days	0.4
Age	74 years	72 years	0.2
Males, %	49%	57%	0.2
White, %	86%	89%	0.4
Charlson Score	2.8 points	2.9 points	0.7
Physical self-maintenance scale (0-30)	23 points	22 points	0.2

RESULTS

	Reductions
All resistant organisms	23%
New MRSA	22%
All Catheter-associated UTI	31%
First new Catheter-associated UTI	46%

ARE SUPRAPUBIC CATHETERS SAFER IN LONG-RUN? PILOT DATA

9 Table 2 Clinical characteristics (i.e. infection, hospitalizations and antibiotic rates)

	Rate, per 1000 device-days		Unadjusted Hazard Ratio	p-value	Covariate-adjusted ^a Hazard Ratio	p-value
	Urethral Catheter	Suprapubic Catheter				
Total population	n = 175	n = 35				
New CAUTI	8.8	6.6	0.82 (0.61 – 1.11)	0.21	0.73 (0.53 – 1.00)	0.05
Hospitalized in past 30 days	6.2	2.4	0.48 (0.29 – 0.78)	<0.01	0.46 (0.32 – 0.67)	<0.01
Antibiotic use in the past 30 days	20.2	15.7	0.85 (0.71 – 1.02)	0.08	0.77 (0.62 – 0.96)	0.02

However, we recovered more MDROs from patients with long-standing suprapubic catheters when compared with urethral catheters

Gibson K et al, J Hosp. Infect 2018 (in press)

HOW MUCH WOULD CAUTI PREVENTION PROGRAMS COST?

Economic Evaluation of a Catheter-Associated Urinary Tract Infection Prevention Program in Nursing Homes

David W. Hutton, PhD,¹ Sarah L. Kruse, PhD, RN,^{2,3} Sanjay Sabot, MD, MPH,^{1,2} Nicholas Graves, PhD,³ Ajay Kulkarni, BS,³ Raymond Lynem, BA,⁴ and Lora Mody, MD, MS,^{1,2,3,4,5,6}

- ✓ CAUTI Prevention Program Cost: 20K/year
- ✓ Most savings come from fewer CAUTI-related hospitalizations
- ✓ 0.197 gain in quality-adjusted life-years

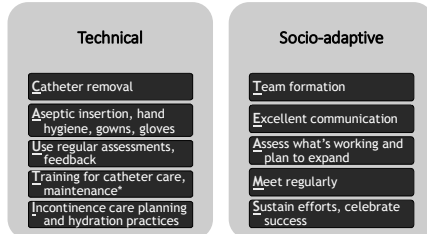
IMPLEMENTATION: SCALING UP

Collaborative approach:

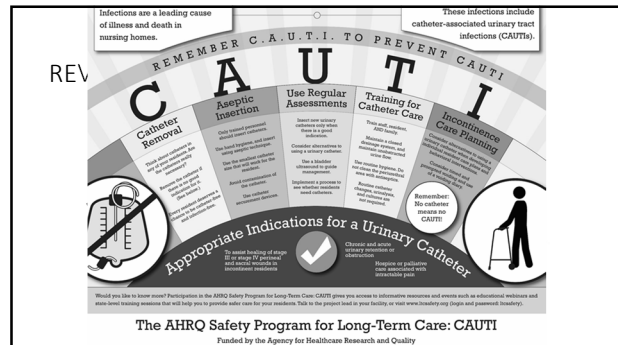
- Address a specific infection or safety concern
- Recruit teams from multiple organizations
- Work in a structured fashion over a limited period
- Narrow gap between best and actual practice

Saint S et. al NEJM 2016;374:2111-9

CAUTI IMPLEMENTATION BUNDLE



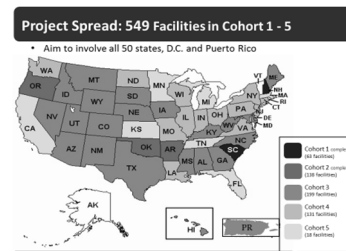
*Included training for appropriate urinary cultures and infection definitions



AHRQ SAFETY PROGRAM FOR LONG-TERM CARE: HAIS/CAUTI



PROJECT SPREAD



OPERATIONALIZING THE INTERVENTION

Educational events

- 4 Onboarding Webinars, study start
- 4 Training Module Webinars, study start
- Content Webinars, monthly
- Coaching Calls with data feedback, monthly
- Organizational Lead calls to discuss implementation, monthly
- 3 Learning Sessions (in-person or web-based)
- Site visits

- Materials:** Videos, power point presentations with notes, easy to use tools, train-the-trainer materials, facility Implementation Guide and LTC Toolkit

Moody L, et al. Clin Infect Dis 2015;61:86-94

DATA COLLECTION, OUTCOMES

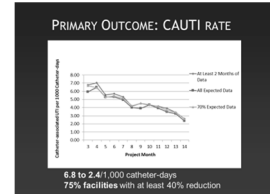
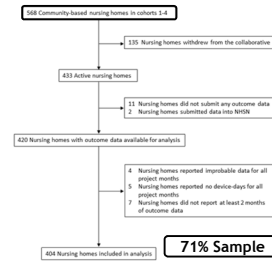
Facility collected:

- # residents (census)
- # residents with an indwelling catheter
- # residents with a CAUTI (per CDC/NHSN definition)
- # of urine cultures ordered at the facility

- Primary Outcome: No. CAUTI/1,000 catheter-days
- Secondary Outcome: Catheter utilization ratio
- Exploratory Outcome: Urinary culture rate/1,000 resident-days

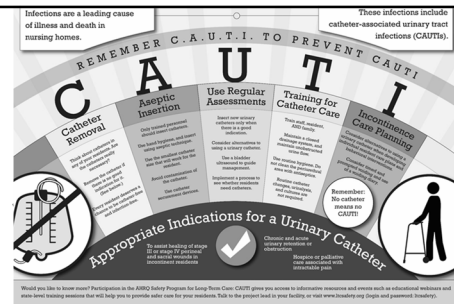
Characteristics	Participating Nursing Homes
Bed size	121
Ownership - %	
For-profit	67%
Non-profit	28%
Government	5%
Part of a chain %	56.3%
5-star Rating	3.5

RESULTS



THE 'ABCDE' OF CAUTI PREVENTION IN HOSPITALS

- A**dherence to general infection control practices (e.g. hand hygiene, surveillance and feedback, aseptic insertion, proper maintenance, education)
- B**ladder ultrasound to guide decision making
- C**ondom catheters, intermittent catheterization should be considered when appropriate
- D**o not use indwelling catheter unless you must!
- E**arly removal of the catheter using a reminder or nurse-initiated removal protocol



The AHRQ Safety Program for Long-Term Care: CAUTI
Funded by the Agency for Healthcare Research and Quality

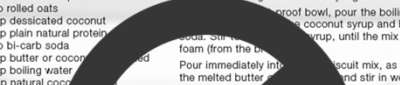
REMEMBER!

- CAUTI prevention is a 'team sport'
- Engage with infection prevention teams and quality improvement initiatives at your institution

Christopher K. Payne, MD
Vista Urology & Pelvic Pain Partners
Emeritus Professor of Urology at Stanford

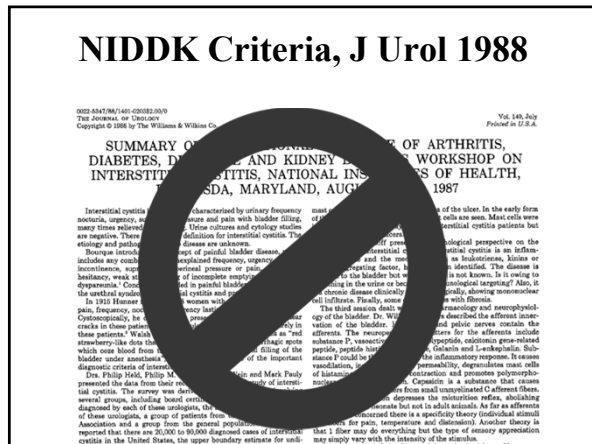
- **Advisory Role:** Avadel, Aquinox, Astellas, Myoforte
- **Ownership Interests:** Vista Urology & Pelvic Pain Partners

- **IC/BPS: Where did we go wrong?**
- **What do we know about these patients?**
- **How should we approach this now?**
- **Future directions (throughout)**

- 
- Heart Healthy Coconut Syrup**
- Ingredients:**
- 1 cup wholemeal spelt flour
 - 1 cup rolled oats
 - 1/2 cup desiccated coconut
 - 1/2 cup plain natural protein
 - 1/2 tsp bl-clar soda
 - 1/2 cup butter or coconut oil
 - 1 cup boiling water
 - 4 tbsp natural coconut syrup
- Instructions:**
1. In a heat mix together all the dry ingredients.
 2. In a separate pot, pour the boiling water into a pot, add the coconut syrup and bl-clar soda. Stir well.
 3. Add the coconut syrup, until the mix starts to foam (from the bl-clar).
 4. Pour immediately into a heat resistant mix, as well as the melted butter or oil and stir in well.
 5. Get a spoonful of the mix, turn your hand, roll into a ball, and press down.
 6. Repeat until you have 12 balls.
 7. Bake in a 180C oven for 10-12mins.
 8. Cool down, then brown.

[illegible]

- **Started with an attractive THEORY**
 - “We believe”
 - “Retrospective Review”
- **Deserved testing**
- **Adopted without question**



Review Article

The Role of Glomerulations in Bladder Pain Syndrome: A Review

Gjertrud E. Wennevik,* Jane M. Meijlink, Philip Hanno and Jørgen Nordling

From the Department of Urology (JNL), University of Copenhagen (GEW), Copenhagen, Denmark, International Painful Bladder Foundation, Rotterdam, The Netherlands (JMM), and Department of Urology, University of Pennsylvania, Philadelphia, Pennsylvania (PH)

Purpose: As a diagnostic marker for bladder pain syndrome/interstitial cystitis, glomerulations were first popularized by Messing and Stamey in 1978. Later this was included in the NIDDK criteria for research and consequently used by many urologists as a default diagnostic criterion. Today the connection between glomerulations and bladder pain syndrome/interstitial cystitis is much debated

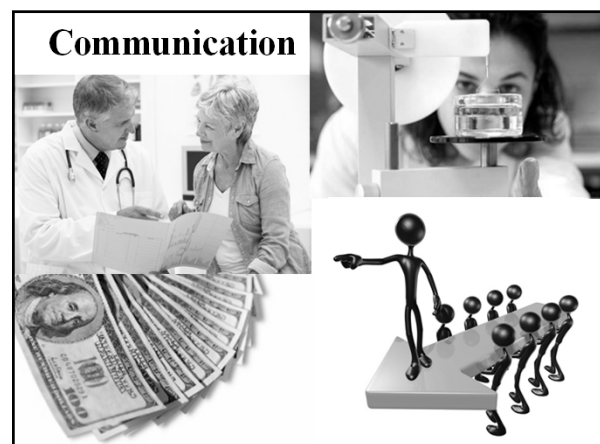
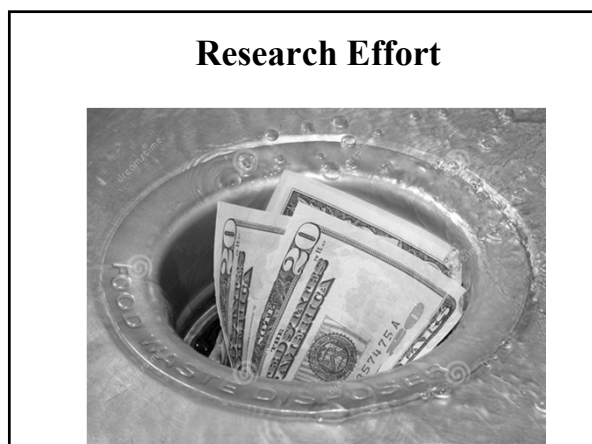
Abbreviations and Acronyms
 BPS = bladder pain syndrome
 ESSIC = International Society for

We found no convincing evidence . . . that glomerulation should be included in the diagnosis or phenotyping of BPS/IC.

J Urol 195:1-7; 2016

So what?

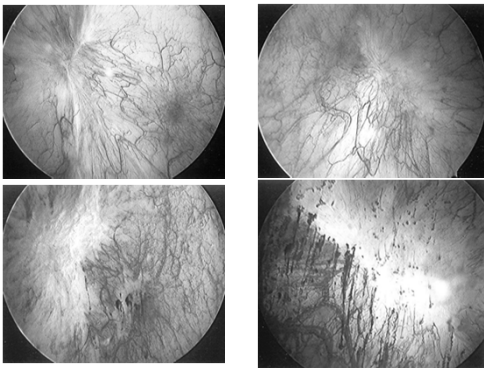
- There isn't anything better
- IC/BPS is good enough until we figure it out.
- Everyone knows it isn't exactly right
- No one really cares about it anyway



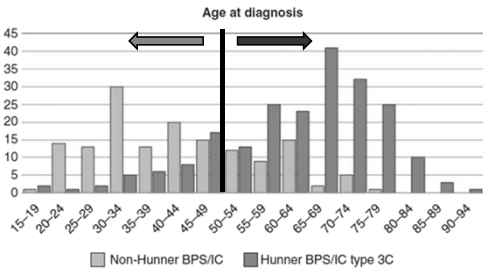
What do we know about these patients today?

- Ulcerative Interstitial Cystitis is a unique, specific disease.
- Bladder Pain Syndrome is not a disease; it is a syndrome.

Ulcerative IC is a disease

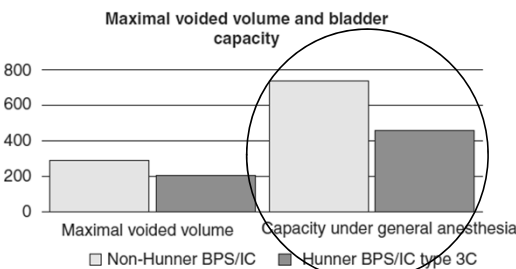


Ulcerative IC is different from BPS



Logadottir Y: Scand J Nephrol Urol 46:365, 2012

Ulcerative IC is different from BPS



Logadottir Y: Scand J Nephrol Urol 46:365, 2012

Bladder Nitric Oxide

Specification of the relevant subtype of 17 patients with IC				
Pt Age - Sex	Measurement 1		Measurement 2	
	Pyl NO	Symptoms	Pyl NO	Symptoms
Classic IC				
77-F	275	Yes		
73-M	255	Yes	1,000	Yes
65-F	1,313	Yes		
65-F	1,504	Yes		
62-F	1,679	No	1,058	Yes
61-F	3,253	No		
60-F	987	Yes		
54-F	2,596	No	2,175	No
41-M	297	Yes	316	Yes
35-F	297	Yes		
Non-ulcer IC				
60-F	1	Yes		
56-M	1	Yes	1	Yes
53-F	1	Yes		
46-F	1	Yes	3	No
44-F	1	Yes	1	Yes
38-F	1	Yes		
20-F	1	Yes		
Control				
66-F	5			
56-F	1			
54-F	1			
36-F	1			
35-M	1			
30-F	2		1	

Logadottir YR: J Urol 2004(171):1148-1151

NO in Ulcer patients:
275-3253ppb

NO in non-ulcer:
1-3ppb

NO in controls:
1-5ppb

Infection/Inflammation

Discovery of Morphological Subgroups That Correlate With Severity of Symptoms in Interstitial Cystitis: A Proposed Biopsy Classification System

Benjamin E. Leiby, J. Richard Landis,* Kathleen J. Propp, John E. Tomaszewski† and the Interstitial Cystitis Data Base Study Group
From the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Purpose: We identified morphologically distinct subgroups in interstitial cystitis using cluster analysis and investigated the associations between cluster membership and urinary symptoms.
Materials and Methods: Of 637 patients enrolled in the Interstitial Cystitis Data Base Study 203 (32%) provided bladder biopsies at baseline screening, representing the focus of this analysis. A cluster analysis algorithm implemented in SAS® PROC CLUSTER using standardized distances to measure the dissimilarity of each pair of patients with respect to select histopathological features was used to construct subgroups of these patients. Multivariate regression models for baseline nighttime and 24-hour voiding frequency, urinary urgency and pain were developed, incorporating indicator variables for cluster membership as predictors. Longitudinal urinary symptom profiles during 3 years of followup were also compared among the morphology clusters.
Results: Three morphology clusters were identified, corresponding to unique pathological groupings. In cluster C₃ 7 patients showed multiple pathological features of parenchymal damage, including several inflammatory features. In cluster C₁ 17 patients was characterized by complete denudation of the urothelium and variable edema. In cluster C₂ in 179 patients none of the pathological features were present above the specified thresholds for C₂. Cluster membership was significantly associated with baseline nighttime and 24-hour frequency (p < 0.001, and with urinary urgency (p = 0.03). These significant increases in baseline symptom severity among clusters from C₂ to C₁ to C₃ persisted throughout the 3 years of followup.
Conclusions: These results suggest an important role for histopathological features in the predictive modeling of interstitial cystitis symptoms.

Key Words: bladder; cystitis; interstitial; biopsy; cluster analysis; urination disorders

Leiby BE: J Urol 2007

Morphological Subgroups of IC

- 203 biopsies, 39 pathologic factors
- 3 subgroups identified by cluster analysis
 - 7 patients with multiple pathological features of parenchymal damage
 - 17 complete denudation, variable edema
 - 179 none of the pathologic features were present above the specified thresholds

Leiby BE, et. al.: J Urol 2007;177: 142-148

Reflect on this a bit



No pathologic abnormality

≠

Chronic inflammatory disease

Ulcerative Interstitial Cystitis

- This is a unique, fascinating, serious disease.
- Many more questions than answers:
 - Histopathologic subtypes
 - Prognosis
 - Optimal medical/surgical therapy
- If we study it we can solve it.

**What do we know now:
BPS is a syndrome**

“A syndrome is a set of medical signs and symptoms that are correlated with each other and, often, with a specific disease.”

Common Syndromes

- Bladder Pain Syndrome
- Head Pain Syndrome
- Chest Pain Syndrome

A syndrome is not a diagnosis. It is a starting point on the path to a diagnosis.

BPS is not well treated without making a more specific diagnosis

My patient has chronic head pain. Should I follow the ANA treatment algorithm?

1. Acetaminophen
2. Sumatriptan
3. Physical therapy
4. Botox injections
5. Brain surgery



Phenotyping Untangles the Mess



Relevant BPS Phenotypes?!

- True Bladder Phenotype
- Myofascial Phenotype
- Pudendal Neuropathy Phenotype
- Central Sensitization Phenotype

Much room for research & refinement

Bladder Phenotype

- What we all learned—pain on bladder filling relieved by urination
- Consistently reduced volumes on diary
- Primary bladder tenderness on exam
- Pain relief with intravesical lidocaine

Myofascial Phenotype

- Often clear provocative factor
- Often other orthopedic issues
- Pain less clearly related to bladder
- Myofascial tender points > bladder, NOT only in pelvic floor
- Bladder diary shows many normal volume voids, especially overnight

Pudendal Neuropathy Phenotype

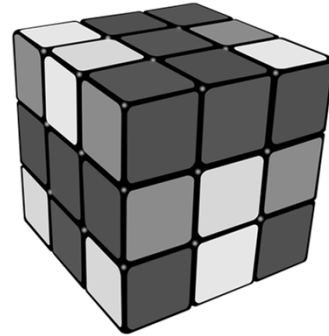
- Pain with sitting
- Specific sensory findings on exam
- Tinel sign over pudendal nerve
- Bladder symptoms less consistent and volumes not always reduced

Systemic Pain Phenotype

“overlapping functional somatic syndrome including fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, chronic headache, and allergies”

Anxiety, Depression, Catastrophizing

How Do We Approach This Now?



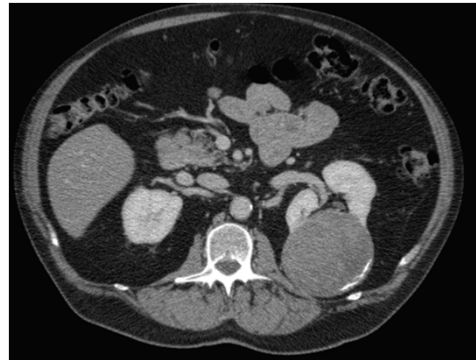
An Oncologic Approach to Interstitial Cystitis/Painful Bladder Syndrome

Christopher K. Payne, MD

**Urology Rounds
University of Pennsylvania
2012**

**Payne CK. Curr Bladder Dysf Reports
March 2015;10(1), pp 81-86.**

Cancer: We attack it



IC: We run from it!



IC as a Cancer

- IC QoL is worse than most other chronic diseases**

Adopt from the Oncologist

- Seriousness of purpose
- Optimistic but realistic approach
- Continuous critical evaluation
- Partnership approach involving the patient

What to Say?

Wrong

- Incurable disease
- Gets worse and worse over time
- Never eat these foods again

Total Nocebo!



What to Say?

Wrong

- Incurable disease
- Gets worse and worse
- You will never be able to eat these foods again

Right

- We don't understand the cause so there is no one cure
- Usually changes very little over the years.
- You should determine if any foods make your symptoms worse

Getting well requires hard work & determination!



The Oncologic Approach

- Diagnosis
- Staging
- Treatment
- Follow-up
- Cure

Diagnosis



Diagnosis: Initial Classification

- Does this patient have ulcerative IC?
- Does this patient have BPS? If so, what is the source of the pain?

History
Physical
Urinalysis/culture
Bladder diary

Interstitial Cystitis Diagnosis

- Cystoscopy
- Hydrodistention
- Biopsy
- Cytology

Diagnosis of BPS (Phenotyping)

- Diagnosis conveys what is known
- Careful, thorough approach
 - Oncologist “rules in” cancer by biopsy
 - We mostly “rule out” other disorders
- The evaluation is individualized to the unique circumstances of each patient

Current Definition BPS

“An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes”

Neurourol Urodyn. 2009;28(4):274-86

ESSIC Approach

The diagnosis of BPS is thus made on the basis of exclusion of confusable diseases and confirmation by the recognition of the presence of the specific combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis (confusable disease or BPS), the presence of a second diagnosis is possible.

van der Merwe JP et. al.: Eur Urol 2008

Table 1 – Confusable diseases for bladder pain syndrome	
Confusable disease	Excluded or diagnosed by ^a
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with	Routine bacterial culture
Common intestinal bacteria	Special cultures
Chlamydia trachomatis, Ureaplasma urealyticum	
Mycoplasma hominis, Mycoplasma genitalium	
Corynebacterium urealyticum, Candida species	
Mycobacterium tuberculosis	Dipstick if “sterile” pyuria culture for M. tuberculosis
Herpes simplex and human papilloma virus	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder-neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or hematuria: upper urinary tract imaging such as CT or IVP
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine, and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound scanning
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic non-bacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis
Pelvic floor muscle-related pain	Medical history, physical examination

CT = computed tomography; IVP = intravenous pyelogram; PSA = prostate-specific antigen.
^a The diagnosis of a confusable disease does not necessarily exclude a diagnosis of BPS.

Diagnosis: Other Testing

- As per ESSIC, as needed to rule out other disorders
- Individualized

Imaging
Urodynamics
Cystoscopy

Staging & Grading

- Oncologists are fanatical about this
- Description is rational
- Evolves with evidence
- Relevant to treatment approach

Neither IC nor BPS have an inherently progressive course

Staging Ulcerative IC

- Bladder capacity under anesthesia
- Number, size of ulcers
- Scarring/distortion of bladder

Staging Ulcerative IC

- Stage 1: >600cc
- Stage 2: 400 to 600cc
- Stage 3: 300 to 400cc
- Stage 4: <300cc

Grading Ulcerative IC

- Interval to recurrence following surgery

Grading Ulcerative IC

- **Grade 1: > 1 year remission**
- **Grade 2: 6-12 months remission**
- **Grade 3: <6 months remission**

Staging BPS

- **Bladder capacity by diary**
- **Objective symptom scores**

STANFORD CENTER FOR NEUROUROLOGY
VOIDING DIARY

2 days, 12 & 13 voids
Mostly 2-6 oz voids
Capacity 20 ounces

01-11-2005 12:00 N
VF1152956

NAME DOB: 03-17-1976 P HSM 703.786-6402
UROL UROLOG MD UROUDYNAMIC (SDT 77)
NEXT APPOINTMENT DATE FIRST INITIALS CROSS PAPER

Day/Date	6am	8am	10am	12pm	2pm	4pm	6pm	8pm	10pm	12am	Midn.	2am	4am	6am
W - 01-11-05	10:30 1.0 L													
T - 01-12-05	1.0 L													
F - 01-13-05														

* PLEASE RECORD THE TIME AND AMOUNT OF EACH VOID FOR AT LEAST TWO DAYS.
* IF INCONTINENCE IS A PROBLEM, TRY TO RECORD WHEN THE LEAKAGE OCCURS.
* IF YOU WEAR PROTECTIVE PADS BECAUSE OF URINE LEAKAGE, MAKE A CIRCLE EACH TIME YOU CHANGE THE PAD.

COP VOID DIARY (Rev 10/96)

Staging BPS

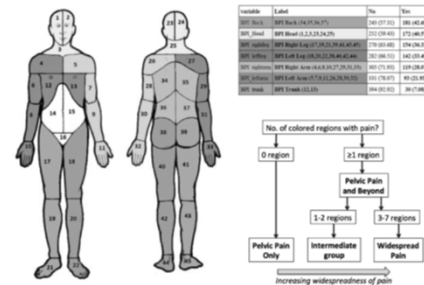


Figure 1. Pain group assignments, including pelvic pain only—0 region, intermediate group with pain beyond pelvis—1 or 2 regions and widespread pain—3 to 7 regions.

Lai HH: J Urol 2017;198(3):622-631

Staging BPS

- **424 patients with pain maps:**
 - 25% only pelvic pain
 - 38% pelvic pain and beyond (1-2 regions)
 - 38% widespread pain (3-7 regions)
- **Correlates strongly with CS**
- **Phenotype or Stage????**

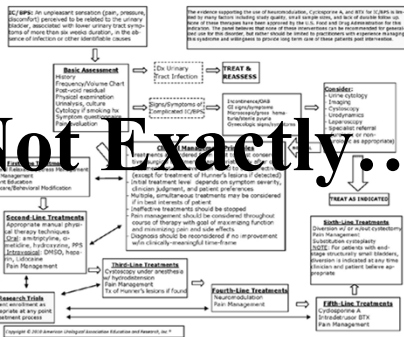
Lai HH: J Urol 2017;198(3):622-631

Treatment of IC/PBS



AUA Guidelines, J Urol 2011

Not Exactly...



Basic/Behavioral Therapies

- Dietary management (Low Fat, Low Sugar, Low Sodium Food List App)
- Bladder training
- General health measures/self care
 - Exercise/fitness
 - Meditation/relaxation

First Line Therapy

- Physical Therapy
- Medical Therapy
 - Amitriptyline
 - Pentosan polysulfate
 - Hydroxyzine
 - Instillation
 - Botulinum toxin

Secondary Options

- Alternative therapies
- Pain management/Referral
- Intraurethral
- Other intravesical
- Botulinum toxin
- Onabotulinum toxin
- Radical

Treatment

- Oncologists know exactly how to use their tools, IC drugs used haphazardly
- Oncologists set a plan for each treatment with specific expectations
- Oncologists evaluate every treatment
- Combination therapy is great . . . when each agent is adding effect.

Treatment of Ulcerative IC

- Ulcerative IC primarily a surgical disease
- Surgery necessary to establish:
 - Diagnosis
 - Stage
 - Grade
- Treatment aimed at restoring normal bladder function

Surgical Treatment of IC

- Distention and fulguration
- Injection of steroids

Adjuvant Treatment of IC

Treatments aimed at the bladder

- Urinary analgesics/bladder training
- Bladder instillations
- Pentosanpolysulfate
- Cyclosporine

Treatment of BPS

- Treatment focused on phenotype
- Each treatment is also a test

Treatment Principles

- One major intervention at a time
- Have a clear plan for each intervention
- Evaluate every intervention subjectively and objectively
 - Symptom score
 - Bladder diary
- Expect to need combination therapy
- Aim for objectively normal bladder

Bladder Phenotype

- Urinary analgesics
- Bladder instillations
- Pentosan Polysulfate
- Pain Management
- Botulinum Toxin
- Neuromodulation

Bladder Training always!

Bladder training

- Efficacy shown years ago by Blaivas
 - If pain reasonably controlled
- Rationale demonstrated by Chai & Keay
 - The distended bladder releases growth hormones
 - Would promote healing
- Involves and empowers the patient

Myofascial Phenotype

- Yoga, stretching, pelvic drop
- Myofascial physical therapy
- Muscle relaxants
- Pain management
- Trigger point injections
- Botulinum Toxin
- Neuromodulation?

Pudendal Neuropathy Phenotype

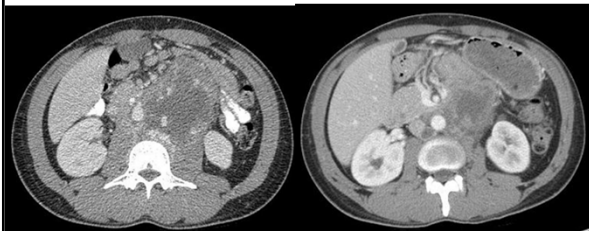
- Stop provocative behaviors
- Yoga, stretching
- Myofascial physical therapy
- Neuromodulating drugs/Pain management
- Injections
- Surgical release/Neurostimulation

Systemic Pain Phenotype

- Team approach—rare urologist who can take this on primarily
- Focus treatment on central sensitization
- Look for untreated anxiety/depression.
- Only when Psych issues addressed should other therapy be instituted.
- Therapy aimed at restoring ADL



Assess the Outcome



The mass has definitely responded but the oncologist will still recommend more therapy

Remission?

- **Complete Remission:**
 - Patient is content
 - No evidence of active disease
 - Normal bladder diary (400cc capacity)
 - No food sensitivities
 - No limitations on activities (exercise, sex)
- **Partial Remission**
 - Patient is content
 - Evidence of active disease
- **Improved—everything else**

Remission! What next?

- The oncologist does not stop therapy when the CT scan shows the lesion disappeared
- Just because we can't see it doesn't mean it is not there
- Consolidation therapy is important:
 - Confirm the good response
 - Normalize behaviors
 - Create expectation of success

CURE

- No oncologist starts off thinking about making the patient a little bit better
- No urologist approaches an IC patient with an intent to cure.
- Could that have something to do with our success??

What is “Cure”?

- Complete remission
- Maintained off medical therapy

Suggest:

1. Maintain the remission for about 6 months
2. Titrate off successful therapies slowly
3. Start with therapy that causes side effects

Five take-home points for managing IC and BPS

1. Ulcerative IC is a disease
2. BPS is not a disease; it is a syndrome
3. Don't think of IC & BPS the same way
4. Don't treat BPS without identifying the pain drivers—phenotyping
5. These are potentially curable diseases

Summary Oncologic Approach

- Adopt the attitude of the oncologist and think of IC as a serious but curable disorder
- Patient participates, sets goals, evaluates
- Emphasize objective assessment and reassessment with diary/symptom scores.
- Assess and document result of each treatment



Male Pelvic Pain NOT prostatitis

Jeannette M Potts, MD
CoFounder
Vista Urology
San Jose, California

Disclosures

Advisory Role

- Aquinox
- Avadel
- Vista Urology



Traveled all over North America seeking help

"Seen" by 13 Urologists

Several courses of cipro, alpha blockers, NSAID's

Traveled all over North America seeking help

"Seen" by 13 Urologists

Several courses of cipro, alpha blockers, NSAID's

AND A HEFTY DOSE OF EMASCULATION

This condition is common

- ICD-9 code 601.1; most common urological dx in men <50
- "Prostatitis more common than BPH and prostate cancer combined."
- "...Will affect 50% of all men at some time during their lives"
- National and Global Prevalence up to 9.7%

CONDITION IS MISNAMED

A LESSON IN
NOMENCLATURE

A LESSON IN
NOMENCLATURE

IMAGINE

NIH Encephalitis Classification

- Category 1: Viral Encephalitis
- Category 2: Bacterial Encephalitis
- Category 3:
- Category 4: Asymptomatic with Abnl CSF

NIH Encephalitis Classification

- Category 1: Viral Encephalitis
- Category 2: Bacterial Encephalitis
- Category 3: **HEADACHE**
- Category 4: Asymptomatic with Abnl CSF

NIH Prostatitis Classification

- Category 1: Acute Bacterial Prostatitis
- Category 2: Chronic Bacterial Prostatitis
- **Category 3 Chronic Pelvic Pain Syndrome**
- Category 4: Asymptomatic/Histological

NIH Prostatitis Classification

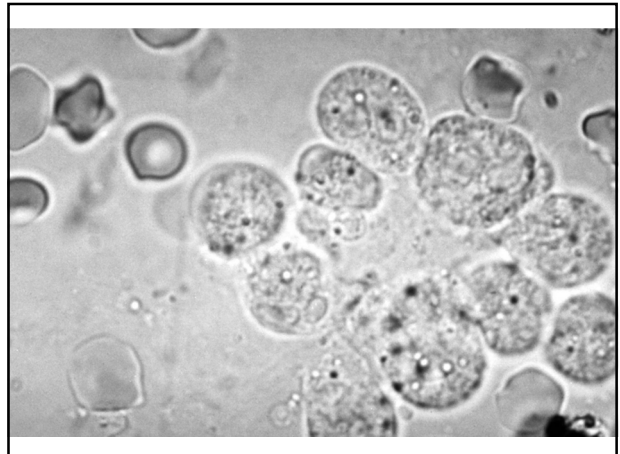
- Category 1: Acute Bacterial Prostatitis
- Category 2: Chronic Bacterial Prostatitis
- Category 3: Chronic Pelvic Pain Syndrome **95%**
- Category 4: Asymptomatic/Histological

Category 3 Prostatitis

never proven to be caused by an infection nor a disease of the prostate.

NIDDK 1996

ONCE UPON A TIME...



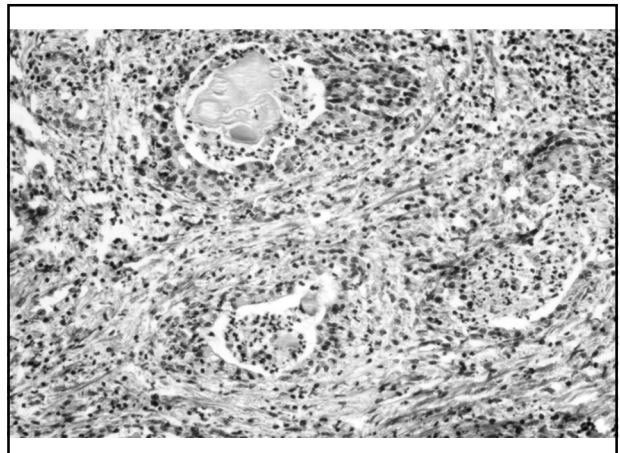
Significance of WBC's in EPS?

- Prostatic inflammation resolves after treatment in acute bacterial prostatitis, but is episodic in chronic and abacterial forms.

Wright, et al. J Urol, 1994

- Among asymptomatic men with elevated PSA, 42% had positive EPS

Potts. J Urol, 2000



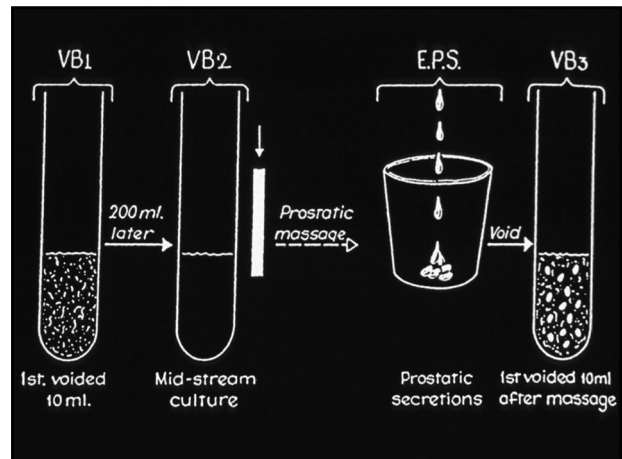
Inflammation Histologically?

- Among SYMPTOMATIC patients, inflammation was identified in only 5%

True, et al. J Urol, 1999

- Among ASYMPTOMATIC patients with elevated PSA up to 52%

Potts. J Urol, 2000



Significance of Bacteria

- Only 5-7 % of patients have positive bacterial cultures.

- 7% of controls have positive bacterial cultures!

Nickel, 2002

- State of the art Micro "Negative in CP/CPPS"

Nickel, AUA, 2013

What if it is a genuine infection?

- Signs or Symptoms
- Fever?
- U/A?
- Culture?
- Treatment?
- Follow Up?

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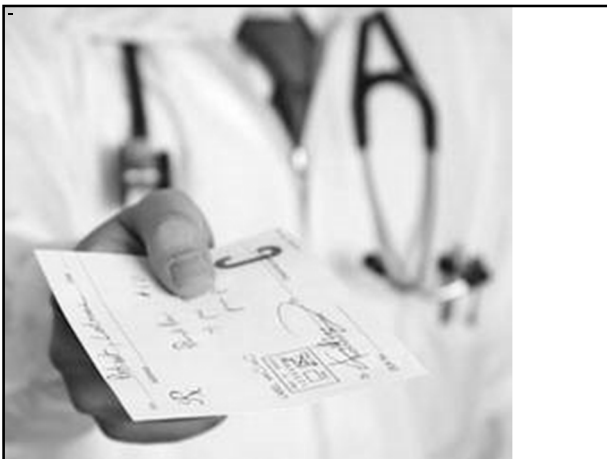
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Use of Meares-Stamey Four-glass Test vs. Antibiotic Use

Always	Almost half	More than half	About half	Less than	Rarely	Never
Meares- Stamey	4%	3%	4%	9%	33%	47%
Antibiotics	40%	42%	9%	4%	4%	1%

McNaughton Collins et al, Urol, 2000

Giessen Consensus

Withhold Antibiotics until there are TWO
corroborative localization cultures

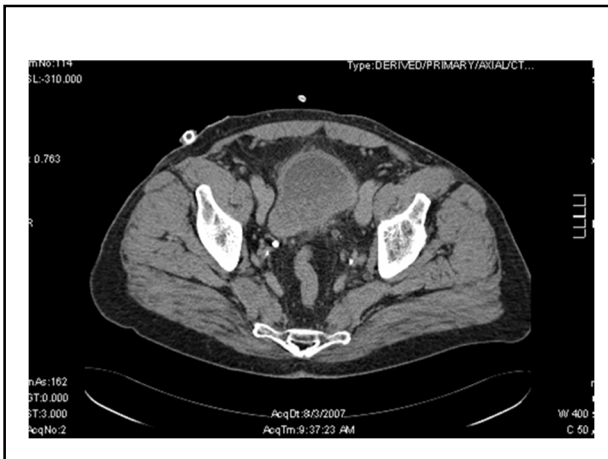
EuropeanUrol Supp, 2002

What if it is a genuine infection?

- Signs or Symptoms
- Fever?
- U/A?
- Culture?
- Treatment?
- Follow Up?

This is a complicated UTI

- Localization Culture
- Imaging
- Exclude obstruction/retention:
 - Flow rate and residual
- Retrograde Urethrogram (RUG)
- Cystoscopy



Randomized Multicenter Feasibility Trial of Myofascial Physical Therapy for the Treatment of Urological Chronic Pelvic Pain Syndromes

Mary P. Fitzgerald,* Rodney U. Anderson,† Jeannette Potts,‡ Christopher K. Payne, Kenneth M. Peters,§ J. Quentin Clemens,||¶ Rhonda Kotarinos, Laura Fraser, Annemarie Cosby, Carole Fortman, Cynthia Neville, Suzanne Badillo, Lisa Odabachian, Andrea Sanfield, Betsy O'Dougherty, Rick Halle-Podell, Liyi Cen, Shannon Chua, J. Richard Landis,** Keith Mickelberg, Ted Barrell, John W. Kusek and Leroy M. Nyberg for the Urological Pelvic Pain Collaborative Research Network

J Urol 182:570, 2009

NIH Multicenter PT Trial

The only POSITIVE study in 15 years.

NIH Multicenter PT Trial

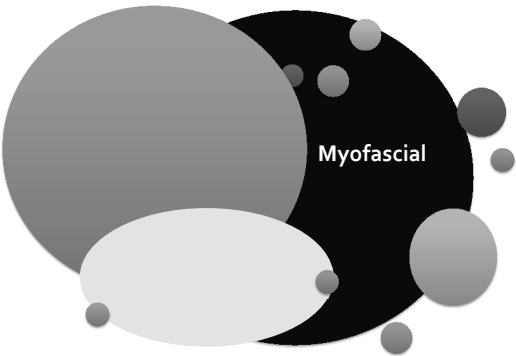
The only POSITIVE study in 15 years.

THE ONLY STUDY TO INCLUDE
Thoughtful, methodical physical examination as
inclusion criteria; ie **PHENOTYPING**.

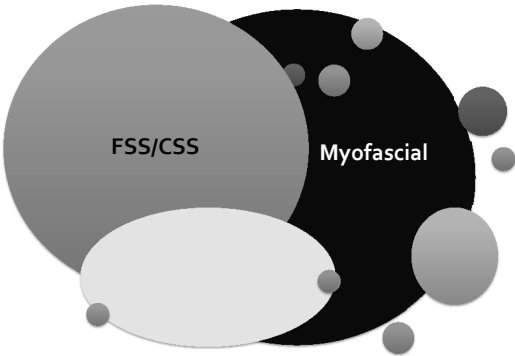
**WE NEED TO CAREFULLY
FORMULATE THE DIAGNOSIS
BEFORE WE TREAT**

**WE NEED TO CAREFULLY
FORMULATE THE DIAGNOSIS
BEFORE WE TREAT
OR STUDY!**

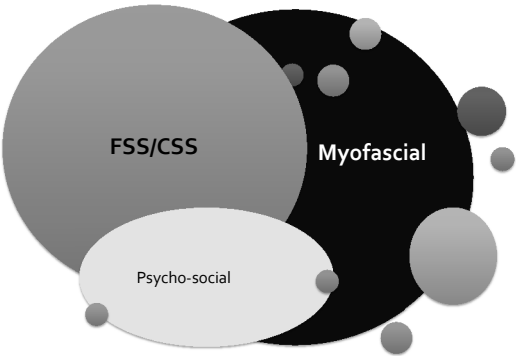
Pelvic Pain Syndrome

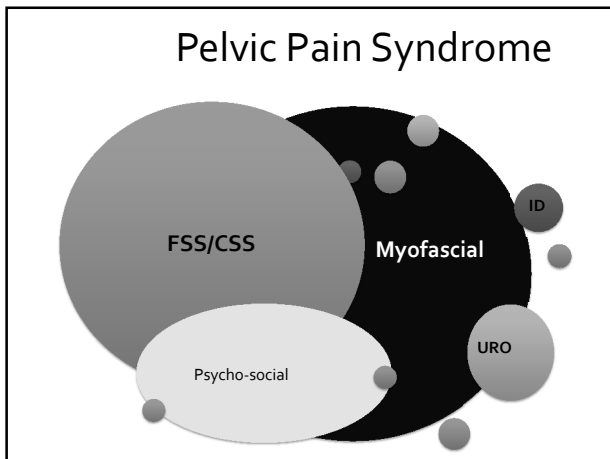


Pelvic Pain Syndrome



Pelvic Pain Syndrome





Beyond the HPI and PMH....
SEARCH FOR FSS/CSS

- ### Functional Somatic Syndromes
- | | |
|----------------------------|---------------------------------|
| ■ Fibromyalgia | ■ Migraine Headaches |
| ■ Irritable Bowel Syndrome | ■ Atypical Chest Pain |
| ■ Proctalgia Fugax | ■ Hyperventilation Syndrome |
| ■ Non-ulcer Dyspepsia | ■ TMJ Syndrome |
| ■ Chronic Fatigue | ■ Interstitial Cystitis |
| ■ Restless Leg syndrome | ■ Multiple chemical sensitivity |
| ■ Globus Syndrome | ■ Gulf War Illness |

“Prostatitis” A functional somatic syndrome

- Psyche-related Dx 48%
- Fnx Somatic Disorders 65%

(Population lifetime prevalence [Bass] 4%)

Potts et al, AUA, 2001
Potts, Euro J Uro, suppl, 2003

“Prostatitis” A functional somatic syndrome

- Psyche-related Dx 48%
- Fnx Somatic Disorders 65%

(Population lifetime prevalence [Bass] 4%)

Potts et al, AUA, 2001
Potts, Euro J Uro, suppl, 2003

CP/CPPS: Comorbidity

BJU 2005	CP=463	Cont=121	P value
urethritis	12%	4%	0.008
Cardiovasc	11	2	0.004
Neuro	41	14	<0.001
Psych	29	11	<0.001
Lymph/heme/inf	41	20	<0.001

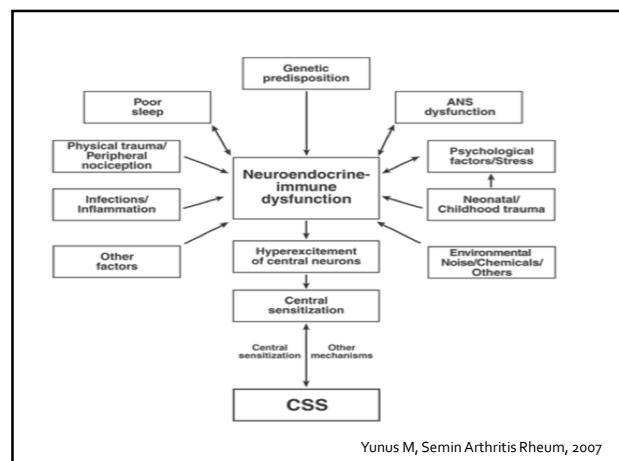
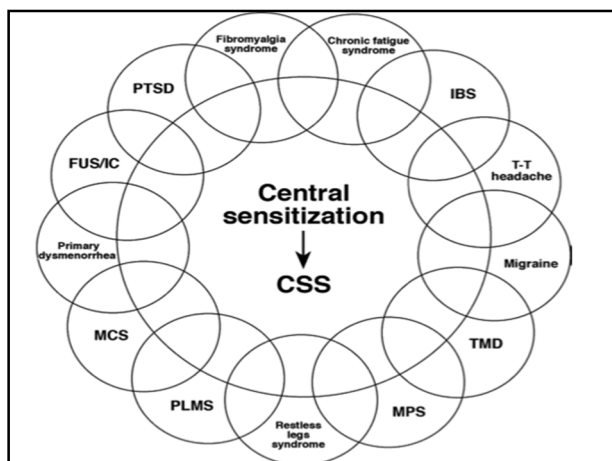
Impact of FSS/CSS

- Prevalence of FSS 4% (Bass, 2002)
- Somatic symptoms and syndromes account for 20-35% of outpatient consultations across all medical specialties (Wessely, 1999)
- US\$256 billion per year in medical care costs are "attributable to the incremental effect of somatization alone." (Barsky, 2005)

CP/CPPS: Co-Morbidity

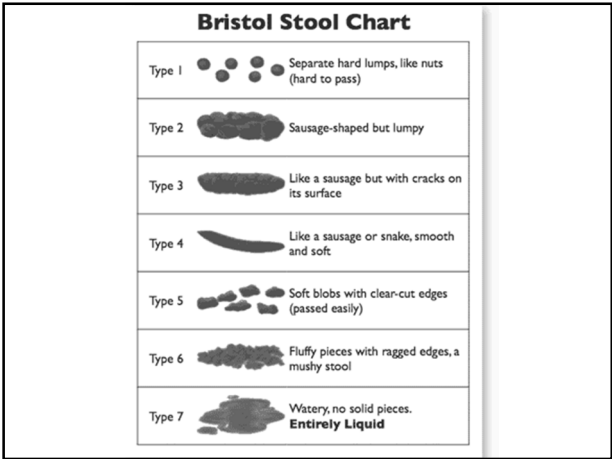
- Annual cost > \$4,000, in US
- Greater healthcare cost than Rheumatoid Arthritis
- Cost differences between CP patients and typical HMO **due to problems other than prostatitis.**

Calhoun et al. Arch Int Med, 2004
Turner et al. Urol, 2004



Yunus M, Semin Arthritis Rheum, 2007



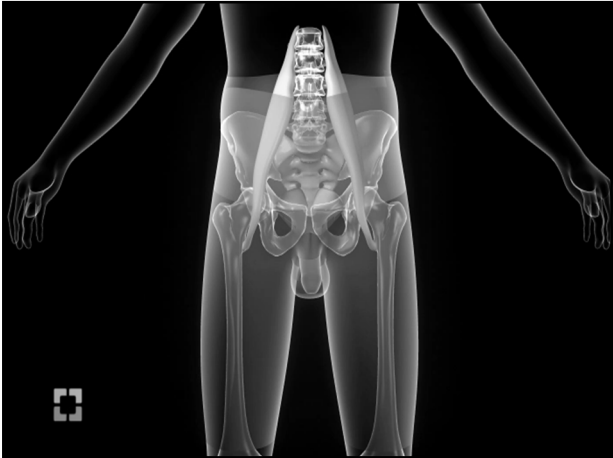


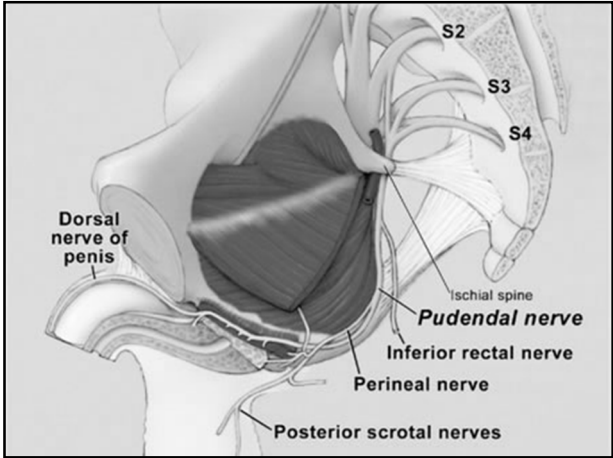
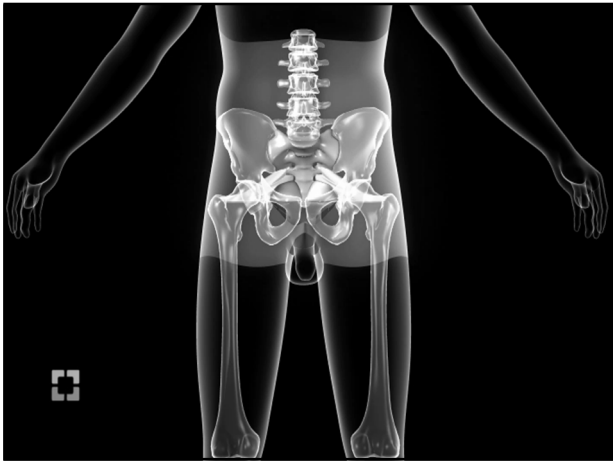
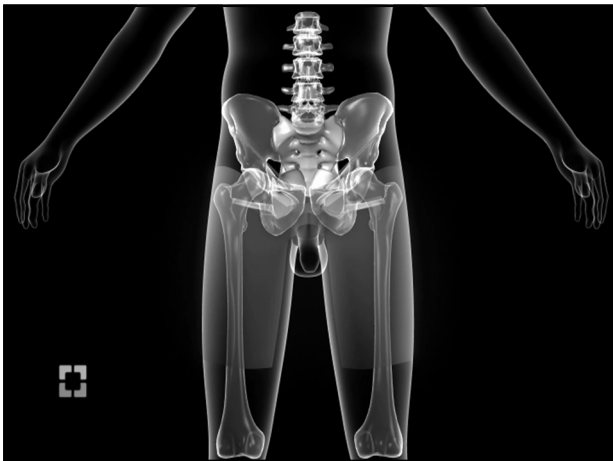
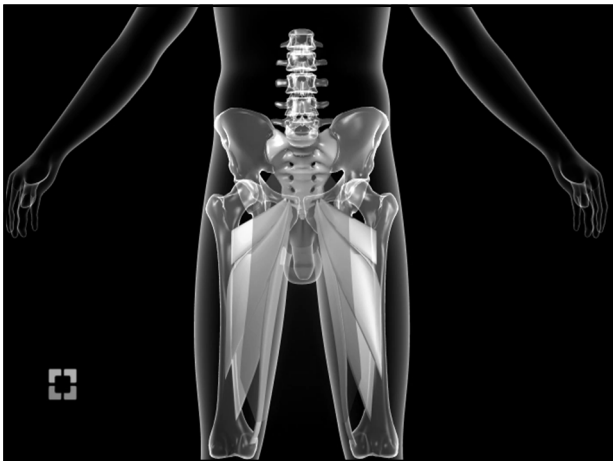
• About 5,840,000 results (0.84 seconds)

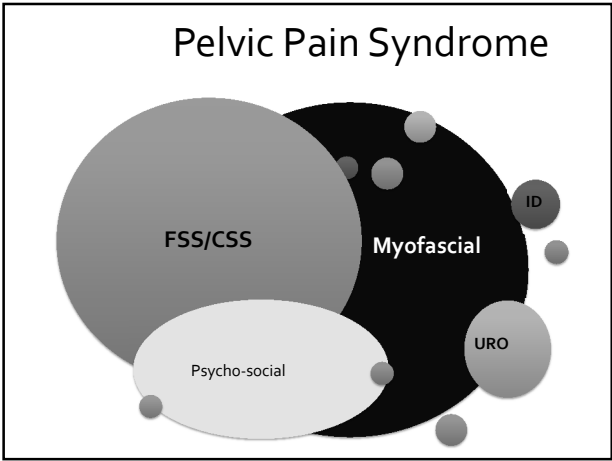
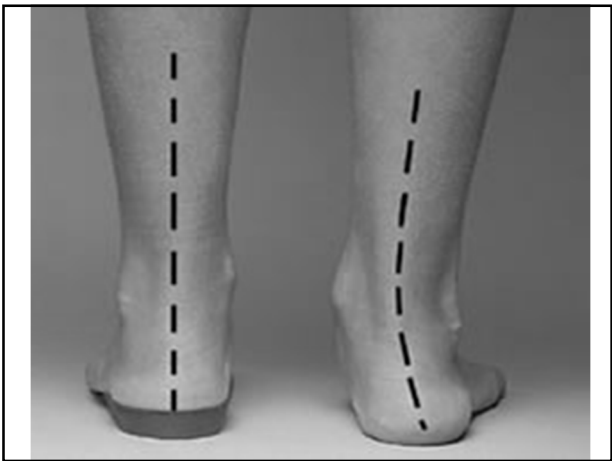
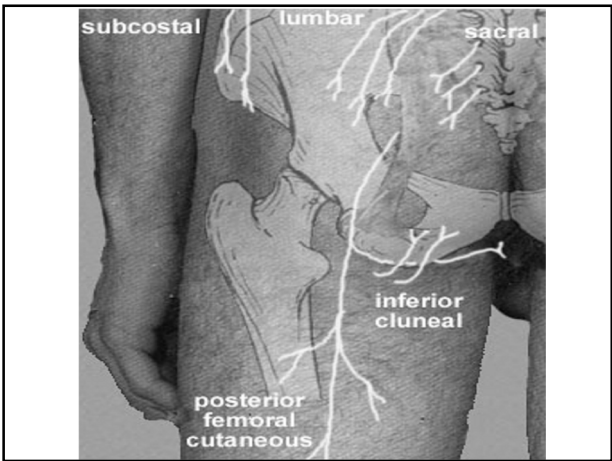
• Ad

- Get Over Porn Addiction - You Can Beat Porn - compulsionsolutions.com
- Address compulsionsolutions.com@BeatPornAddiction@53 535 446
- Caught By Internet Porn? Could It Be Addiction? Get Confidential Help Here
- Sex Addiction Therapy - Porn Addiction Help - Masturbation Addiction - Internet Addiction
- Online Course/Contact Us/Free Book Excerpt/Our Services
- Search Results
- How to Stop Porn Addiction - One Powerful Technique to Help You ...
- www.feedthehighwall.org/using/how-to-stop-porn-addiction-stop-watching-porn/
- May 27, 2018 - Right now, you are looking at the same page I was (How to Stop Porn Addiction) when I was at my lowest point ... I was suicidal, I got fired, ...
- How to Quit Porn: 6 Essential Steps | by Dr. Doug Weiss
- www.careempathy.com/2018/03/how-to-quit-porn-6-essential-steps/
- Apr 23, 2012 - "You have to decide that you are worth living porn free." Sex addiction expert Dr. Doug Weiss shares 6 important steps on how to quit porn.
- How to Overcome Porn Addiction and Get Your Life Back
- www.uncommonhelp.me - Addiction Help
- How do you tell if you're actually addicted to porn? Well, if you feel it controls you and you regularly view porn for hours and often feel you can't stop, if it affects ...
- Breaking a Pornography Addiction - LDS.org
- https://www.lds.org/youth/article/breaking-a-pornography-addiction?lang=eng
- I've become addicted to pornography. It's ruining my life. What can I do to break the addiction? Pornography is a widespread and serious problem. It hurts your ...
- Three Apps to Break a Porn Addiction | CNN News - CNN.com
- www.cnn.com/2016/05/10/tech/apps/three-apps-to-break-a-porn-addiction
- Apr 1, 2016 - Years ago, getting a hold of pornography wasn't that easy. People would secretly purchase a dirty magazine or obtain a video from the wrong ...
- How to Deal With Porn Addiction (with Pictures) - wikiHow
- www.wikihow.com - ... Health - Conditions and Treatments - Addictions
- Nov 3, 2015 - Pornography addicts use porn as a way to cope with boredom, anxiety, ... Some people may want to stop porn consumption altogether, while ...
- 3 Ways to Avoid Pornography - wikiHow
- www.wikihow.com - ... Health - Conditions and Treatments - Addictions
- If you want to avoid pornography, read this wikiHow - ... Alternatively use Stop Procrastinating App that allows you to block internet access or filter ... offers users goal setting options to help them focus
- psychography on breaking their addiction
- 10 Steps to Overcoming Pornography Addiction | Growtreat: Marriage
- www.growtreat.com/overcoming-pornography-addiction/
- Dec 30, 2015 - 10 Steps to Overcoming Pornography Addiction: 3 Ways to Help Your Husband with His Anger: What is Not Okay in Bed? Masturbation: The ...
- Porn addiction How To Break internet porn addiction - YouTube

BEYOND THE ROUTINE EXAM...







**IF PATIENT DOES NOT IMPROVE
START OVER- FROM SCRATCH**

Male Infertility

C. Tanrikut, MD, FACS
Reproductive Urologist, Shady Grove Fertility
Georgetown University School of Medicine



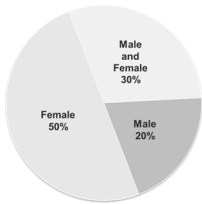
Disclosures

- Medical Director, Andrology Laboratory of New England Cryogenic Center
- Advisory Board, Ferring Pharmaceuticals
- *Off-label medication use

Objectives

- To provide a thorough understanding of male reproductive anatomy and physiology
- To discuss the rationale and approach to evaluation of the infertile male
- To explain treatment approaches for male factor infertility

Infertility

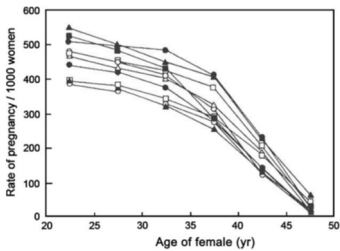


- 25% pregnant after 1 month of trying, 85% after 1 year
- Infertility is present in 10-15% of all couples
- Attributable to male factor in 50% of cases

Anderson et al, Fertility and Sterility 2009

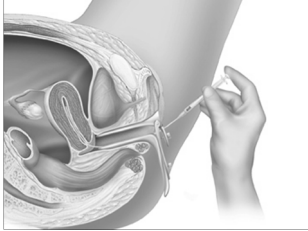
What does a urologist need to know about the female partner?

Trends in Fecundity

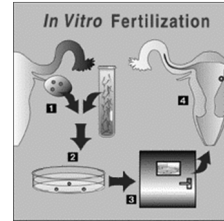


Adapted from the Practice Committee of ASRM, 2008

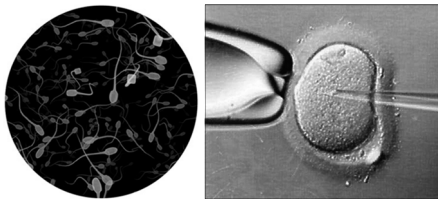
Intrauterine Insemination (IUI)



In Vitro Fertilization (IVF)



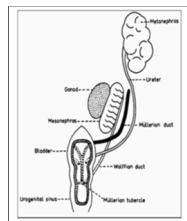
ICSI: one sperm per egg



Back to Basics: Anatomy and Physiology

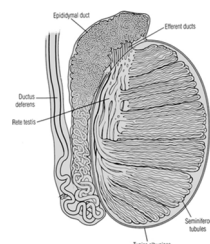
Embryology

- Wolffian (mesonephric) duct (T-mediated):
 - Body/tail of epididymis
 - Vas deferens
 - Seminal vesicle
 - **Mesonephros is precursor to metanephros...
- Müllerian duct involution under the influence of Mullerian-inhibiting substance



Testicular Anatomy

- Cremasteric muscle
 - Temperature control
- Connective tissue
 - Tunica albuginea
 - Fibrous septae
- Seminiferous tubules
 - 2-4 loops/lobule
 - 300m total length
 - Empty into rete testis
- Efferent ducts
 - ~6-12 drain into epididymis



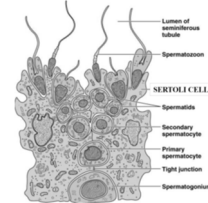
Testicular Anatomy

- Functional
 - Endocrine function – Leydig cells
 - Exocrine function – Sertoli cells
- Structural
 - Intratubular compartment
 - Sertoli cells
 - Germ cells
 - Peritubular compartment
 - Leydig cells
 - Basement membrane
 - Myofibroblasts
- Blood-testis barrier



Sertoli cells

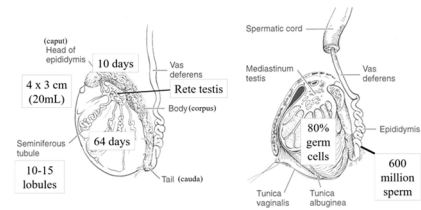
- Polarized cells: extend from basement membrane to lumen
- Comprise 1/3 of bulk of germinal epithelium
- Responsible for blood-testis barrier
- Engulf and nurture developing germ cells
- Regulate tubule microenvironment (govern fluid secretions, phagocytosis, steroid metabolism, sperm production, and sperm movement/development)



Synopsis of Leydig and Sertoli cell synergy

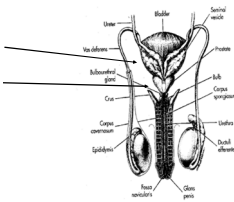
- What role do Leydig cells play in creating a favorable environment for sperm production?
 - Testosterone production in response to LH
 - Paracrine effect on Sertoli cells
 - Testosterone concentration in testes ~100x peripheral serum concentration
- How do Sertoli cells support spermatogenesis?
 - FSH stimulates Sertoli cell function throughout life
 - Create a specialized microenvironment
 - Expose germ cells to high levels of testosterone
 - Transport differentiating germ cells toward the seminiferous tubule lumen

Timeframe of sperm production: ~2.5 mos

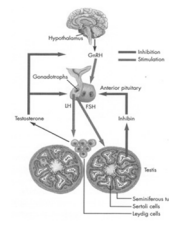


GU Anatomy – Semen Composition

- Seminal vesicles
 - 1.5 ml, alkaline
 - Fructose
- Prostate
 - 0.5 ml, acidic
- Testis, epididymis
 - 0.1 ml
- Cowpers glands
- Perurethral glands



HPT axis



GnRH → LH and FSH production

LH – Leydig cells → Testosterone

FSH – Sertoli cells → Spermatogenesis

Negative feedback by:
Testosterone → Estradiol, DHT
Inhibin

Chief Complaint

"My partner and I really want to have a baby – we've been trying for a year without success. Can you help us??"



History

- Prior fertility
- Sexual function: drive, erectile, ejaculatory
- Testis pain or swelling
- Cryptorchidism
- Prior inguinal or scrotal surgery, trauma
- Brothers' fertility history

Medications

- Calcium channel blockers
- Gout medications
- Cimetidine
- Sulfasalazine
- Exogenous testosterone
- ?finasteride
- (Alpha-blockers)

Social History

- Heat exposure
- Exercise
 - Anabolic steroids?
- Tobacco
- Alcohol
- Illicit drugs
- Lubricants

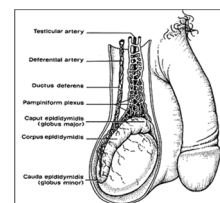
Physical Examination

- Body habitus
- Hair distribution
- Gynecomastia
- GU exam



GU Anatomy -- Exam

- Phallus
- Testes
- Epididymides
- Spermatic cord
 - Vasa deferentia
 - Varicocele



Hypogonadism

"Inadequate gonadal function, as manifested by deficiencies in gametogenesis and/or the secretion of gonadal hormones" (Stedman's Medical Dictionary, 27th edition)

- Poor function of the testes
 - Diminished sperm production
 - Decreased testosterone production
- Two basic causes
 - Problem with the testes
 - Problem with the signals to the testes

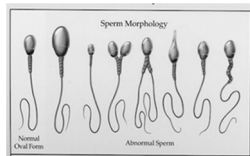
Testing

- Semen Analysis
- Bloodwork
 - Serum endocrine studies
 - (Genetic testing)
- [Imaging]
 - (Scrotal U/S)
 - (Transrectal U/S)

Semen Analysis

- Volume
- pH
- Concentration (#sperm/mL)
 - oligospermia
 - azospermia
- Motility
 - asthenospermia
- Morphology
 - teratospermia

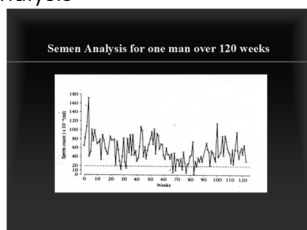
**2.5 day abstinence interval



SA reference values – WHO 5th Ed. (2010)

- Volume ≥ 1.5 cc
- pH ≥ 7.2
- Sperm concentration ≥ 15 mil/mL
- Sperm count ≥ 39 mil/ejaculate
- Motility $\geq 40\%$ TM, $\geq 32\%$ PM
- Morphology $\geq 4\%$ (strict)

Semen Analysis



Male Infertility and Azoospermia

- Azoospermia = absence of sperm in ejaculate
 - Identified in ~10-15% of infertile males
 - (<2% of overall male population)
- Etiologies of azoospermia
 - Production issue
 - Primary hypogonadism ~60%
 - intrinsic disorder of spermatogenesis
 - Secondary hypogonadism (rare)
 - Outflow issue
 - Blockage or EJD ~40%



Algorithm for evaluation and treatment of azoospermia



[http://www.aunet.org/guidelines/male-infertility-azoospermic-male-\(reviewed-and-amended-2011\)](http://www.aunet.org/guidelines/male-infertility-azoospermic-male-(reviewed-and-amended-2011))

SA characteristics in azoospermia

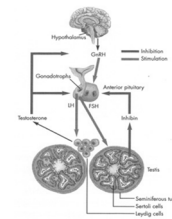
	[sperm]	volume	pH	fructose
NOA	azoospermia	normal	normal	normal
8 epi obstruction	azoospermia	normal	normal	normal
CBAVD	azoospermia	normal or low	normal or low	normal or low
EDO	azoospermia	low	low	absent

NOA = nonobstructive azoospermia
CBAVD = congenital bilateral absence of the vasa deferentia
EDO = ejaculatory duct obstruction

Endocrine Profile

- Testosterone (AM draw)
- Follicle stimulating hormone
- Luteinizing hormone
- Estradiol
- Prolactin
- Thyroid Stimulating Hormone

HPT axis



GnRH → LH and FSH production

LH – Leydig cells → Testosterone

FSH – Sertoli cells → Spermatogenesis

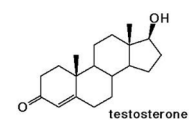
Negative feedback by:
Testosterone → Estradiol, DHT
Inhibin

Endocrine Profiles in Hypogonadism

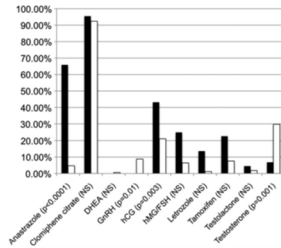
Endocrine status	T	FSH	LH	PRL
Primary hypogonadism	low	HIGH	HIGH	Normal
Secondary hypogonadism	low	low	low	Normal
Hyperprolactinemia	low	low	low	HIGH
Androgen resistance	HIGH	HIGH	HIGH	Normal

Testosterone replacement

- Downregulates GnRH
 - ↓FSH, ↓LH
- Suppresses spermatogenesis
 - Oligospermia
 - Azoospermia
- Recovery to "normal" sperm concentrations within one year...but may not return to baseline



We are our own worst enemies



Ko et al. J Urol 2012

T optimization: whom to treat?

- T <400 ng/dL
- Sexual dysfunction
- Suboptimal semen parameters
- ?Consider in those with recent history of testosterone/anabolic steroid use

T optimization – how to treat?

- *Clomiphene citrate
- *Anastrozole
- hCG +/- FSH

Clomiphene citrate*

- Blocks estrogen feedback at level of hypothalamus and pituitary
 - Increases production of FSH and LH
 - Stimulates testicular function
- Dosing:
 - 50 mg every other day
 - 50 mg TIW
 - 25 mg daily

*(off-label use)

Whitten et al. Fertil Steril 2006

Aromatase Inhibitors*

- Blocks conversion of testosterone to estradiol
 - Increase in Testosterone
 - May see increase in FSH and LH due to lack of negative feedback by estradiol
- Dosing:
 - Anastrozole 1 mg daily

*(off-label use)

Raman and Schlegel, J Urol 2002
Roth MY et al. Nat Clin Pract Endocrinol Metab 2008

Gonadotropin Treatment

- hCG stimulates Leydig cells (same action as LH)
 - 1000-3000 U 2-3x weekly
- FSH stimulates Sertoli cells
 - FSH 75-150 U 3x weekly
- hMG (LH+FSH) 75-150 U 2-3x weekly

Liu PY et al. J Clin Endocrinol Metab 2009

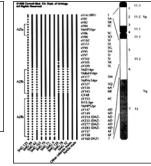
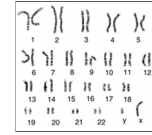
Hypogonadotrophic hypogonadism (e.g., prior pituitary surgery, Kallmann Syndrome)

- Low FSH
 - Low LH
 - Low serum T
 - [normal PRL]
 - [normal pituitary MRI]
- Treat with gonadotropins (can consider clomiphene in mild cases)

Genetic testing

Production-related (azoospermia, severe oligospermia)

- Karyotype
 - Klinefelter syndrome (47XXY)
 - Robertsonian translocations
 - Reciprocal translocations
- Y microdeletions (long arm)
 - AZFa, AZFb → no sperm
 - AZFc → sperm extraction



Obstruction-related (azoospermia/absent vasa)

- CFTR testing

Klinefelter Syndrome

- 1:500-1:1000 live male births
- Majority nonmosaic, fewer mosaic (46XY/47XXY)
- Hallmark: atrophic testes, primary hypogonadism
 - Elevated FSH
 - Low or low-normal serum T
 - Decreased germ cell mass, azoospermia
 - Associated with diabetes, learning disabilities, increased risk for breast cancer, non-Hodgkin lymphoma

Congenital Bilateral Absence of the Vasa Deferentia

- Accounts of 6% of cases of obstructive azoospermia
- Most common cause = mutation of CFTR gene (chromosome 7) for transmembrane transport chloride ion transport
 - Common mutation, leading cause of CF = Δ508 – 70% mutations
 - Almost all males with CF will have CBAVD
 - ~70-80% of men with CBAVD have no clinical evidence of CF
 - Over 500 possible mutations
- Diagnosis
 - Physical examination
 - Prominent epidymis
 - Absent distal 2/3 of epididymis
 - Atrophy/hypoplasia of seminal vesicles
 - Imaging and surgical exploration not necessary to confirm diagnosis
- Men with CBAVD should be offered genetic testing and counseling, as well as their female partners
- Imaging for renal anomalies should be offered in those with unilateral vasal agenesis or CBAVD and no evidence of CFTR abnormalities

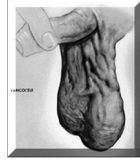
Male Reproductive Surgery

Surgically-treatable Male Factor Issues

- Varicocele
- Obstruction
 - Vasectomy
 - Congenital absence of vasa deferentia
 - Infection
 - Iatrogenic (e.g., previous hernia repair)
 - Prostate utricle/Mullerian duct cyst, SV cysts
- Spermatogenic dysfunction

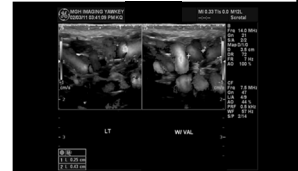
Varicocele incidence

- 15% in general population
- 35% with primary infertility
- 80% with secondary infertility
- L>R
- 15-50% cases bilateral
- Isolated right varicocele fairly rare



Varicocele evaluation

- Physical examination
 - Visualization of veins: "bag of worms"
 - Palpation of veins within spermatic cord
- Doppler U/S



Varicocele Grading System

Grade	Physical Exam
1	Palpable on exam only w/ Valsalva
2	Palpable on exam without Valsalva
3	Visible on exam

Varicocele – intervention

- Male factor infertility
 - Oligospermia, asthenospermia
- Testicular size differential
- (Pain)
- (Consider for low testosterone)
- Adult men with palpable varicocele and normal SA/bloodwork may be followed with periodic testing

Varicocele – treatment options

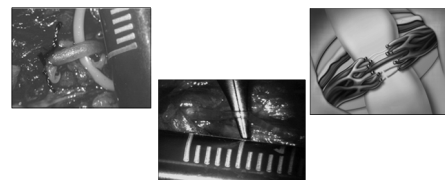
- Retroperitoneal
- Inguinal or subinguinal varicocelectomy
- Microsurgical varicocelectomy
- Laparoscopic varicocelectomy
- Percutaneous embolization

Table 1 Outcomes of varicocele treatment

Type of repair	Pregnancy rate (%)	Recurrence rate (%)	Hydrocele rate (%)
Open (all types) (22)	29	14	0.1
Open (inguinal) (21)	31	11	3
Laparoscopic (22)	30	17	0.08
Open microsurgical (23)	40	2	0 (0.005)
Sclerotherapy (retrograde) (30)	42	11	0
Sclerotherapy (retrograde) (30)	30	11	0

Velasquez and Tanrikut, *Transl Androl Urol* 2014

Microsurgical varicocelectomy

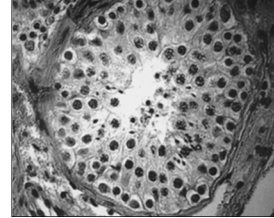


Images courtesy of Marc Goldstein, MD

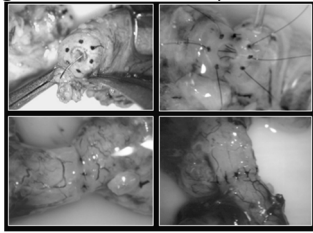
Impact on Testicular Function

- Significant improvement in semen parameters in 60-80% of men
 - Greater improvement associated with larger grade varicocele and poorer starting parameters
- Reported pregnancy rates 30-60%
- Prevention of progressive functional decline
- Cost-effective
- T impact:
 - Comhaire and Vermeulen (*J Clin Endocrinol Metab*, 1975)
 - Serum testosterone levels returned to normal after varicocelectomy
 - Su et al. (*J Urol*, 1995)
 - Significant improvement in testosterone production post-varicocelectomy
 - Tanrikut et al. (*BJU Int*, 2011)
 - Significant increase in post-op T levels in more than 2/3rds of patients

Obstructive azoospermia



Microsurgical vasovasostomy



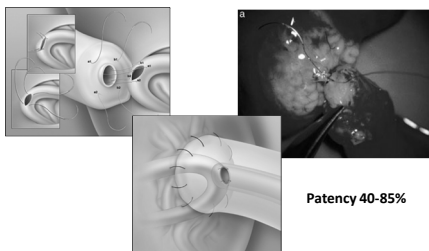
Images courtesy of Marc Goldstein, MD

Vasovasostomy outcomes

- Patency rates: 70-95%
 - **Length of time since vasectomy
 - Presence of sperm intraoperatively in vasal fluid
 - Gross appearance of vasal fluid
 - Length of vasal segment between epididymis and vasectomy site
 - Presence of sperm granuloma
- Paternity rates: 30-75%
 - Female partner age is most important determining factor



Microsurgical vasoepididymostomy

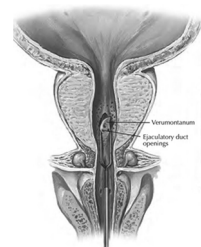


Patency 40-85%

Chan PTK et al, *BJU Int* 2005

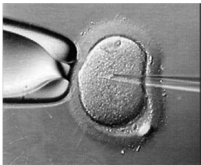
Transurethral Resection of Ejaculatory Ducts (TURED)

- Diagnosis of EDO:
 - Low-volume, low-pH (<7.2), fructose-negative azoospermia
 - Dilatation seen on TRUS
 - SV aspirate +sperm
- Sperm return to ejaculate in 50-75%
- Conception rate ~25%

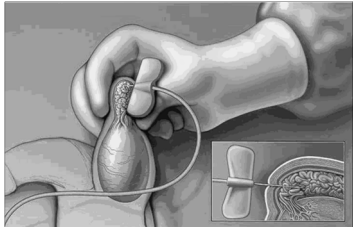


Sperm Extraction

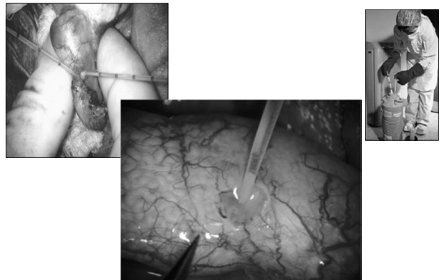
- Epididymis
 - microsurgical
 - percutaneous
 - Testis
 - open biopsy
 - percutaneous
- Necessitates IVF-ICSI!!!**



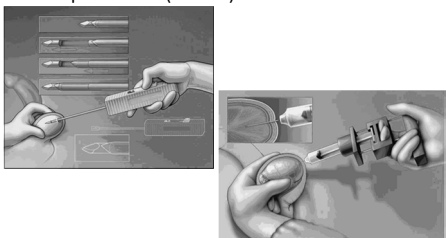
Percutaneous Epididymal Sperm Aspiration (PESA)



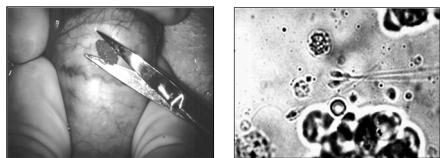
Microsurgical Epididymal Sperm Aspiration (MESA)



Percutaneous Testis Biopsy or Testicular Sperm Aspiration (TESA)



Open Testis Biopsy



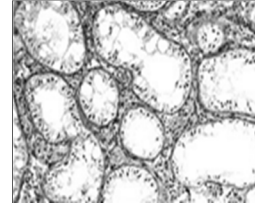
Sperm Extraction Techniques

	Advantages	Disadvantages
Microsurgical epididymal sperm aspiration (MESA)	•Large quantity of sperm obtained for several IVF/ICSI cycles in 1 procedure	•Requires microsurgical skills •Incision w/ post-op discomfort •Higher cost compared to percutaneous procedures
Percutaneous epididymal sperm aspiration (PESA)	•No microsurgical skills required •Fast •Minimum post-op discomfort	•Fewer sperm retrieved •Risk of epididymal damage
Testicular sperm extraction (TESE) and microTESE	•Large quantity of sperm obtained for several IVF/ICSI cycles in 1 procedure •Often used when epididymal sperm are not motile	•Risk of testicular damage w/ multiple biopsies •Incision w/ post-op discomfort •Higher cost compared to percutaneous procedures
Percutaneous testicular sperm aspiration (TESA)	•No microsurgical skills required •Fast and easy •Minimum post-op discomfort •Minimally invasive	•Fewer sperm retrieved

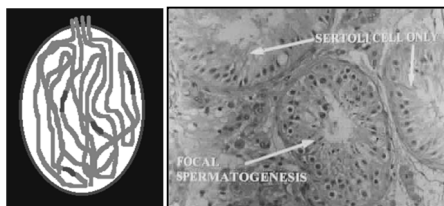
Vas Reversal versus Sperm Extraction

Vasectomy Reversal	SSR + IVF/ICSI
• Obstructive Interval < 15 years	• Advanced female age is present
• No female fertility risk factors present	• Female factors requiring IVF are present
• Couple may be willing to wait 1.5 years	• Chance for success for SSR + IVF/ICSI exceeds the chance for success w/ surgical treatment
	• SSR + IVF/ICSI is preferred by the couple for financial reasons

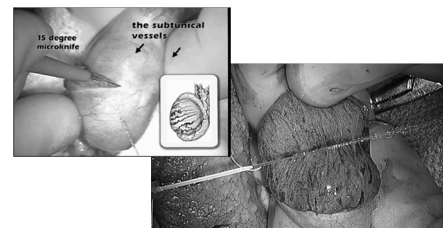
Non-obstructive Azoospermia



Non-obstructive Azoospermia

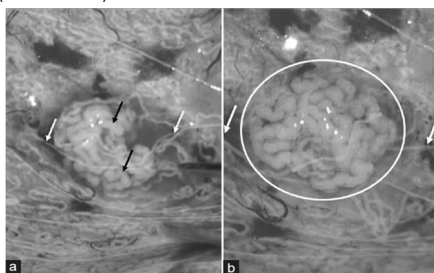


Microdissection Testicular Sperm Extraction (MicroTESE)



Images courtesy of Peter Schlegel, MD

Microdissection Testicular Sperm Extraction (MicroTESE)



Conclusions

- A good understanding of male reproductive anatomy and physiology is essential to effectively evaluating and treating male fertility patients
- There are medical and surgical treatment options available for most men with male factor infertility
- Female partner age is the most important predictive factor in terms of likelihood of conception
- Important to counsel patients regarding all treatment options as well as the timeline to treatment

Erectile Dysfunction: Exploring Options for Treatment

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Disclosure Statement: In accordance with ACGME policy on relevant financial disclosure, I disclose financial relationships with the following entities:

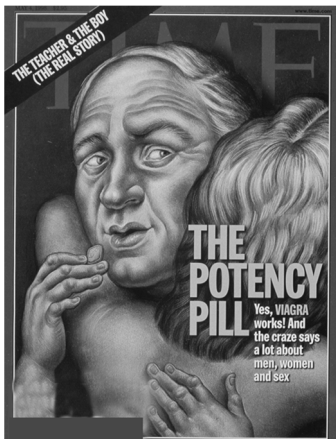
Research Grants: Boston Scientific, Astellas
Expert Testimony: Abbvie

Rise of Sexual Medicine: History Highlights I

- Antiquity
- India, circa 1000 B.C.
- Greece, circa 320 B.C.
- China, 300 B.C.
- Rome, circa A.D. 50
- Europe, circa 1350
- Rhinoceros horn Oysters
- Rock salt
- Ram testicle, boiled in milk
- Satyrion (plant)
- Cloves
- Ginger ointment
- Dried black ants and olive oil
- Jackal bile ointment
- Melted fat from camel humps ointment
- Rotten leeches ointment
- Ground-up Spanish fly ointment/potion

Rise of Sexual Medicine: History Highlights II

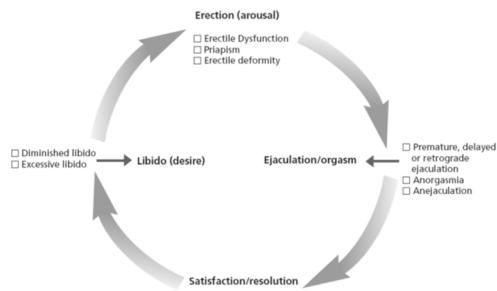
- 1912
- Early to mid-1900's
- 1936
- 1952
- 1954
- 1967
- 1973
- 1983
- Psychoanalysis (Sigmund Freud)
- Yohimbine
- Cartilage implant (Bogoras)
- Acrylic splint implant
- Sex-therapy (Masters & Johnson)
- Vacuum-pump technology
- Penile revascularization (Michal)
- Intracavernous pharmacotherapy (Brindley/Virag)
- Caverject (alprostadil)
- Intraurethral alprostadil
- PDE5 inhibitor therapy



Overview

- Management principles
- Diagnostic evaluation
- Treatment considerations

The Male Sexual Response and Associated Disorders



Fine SR. J Am Osteopath Assoc 104(Suppl 1):S9-15, 2004.

Management Principles

- Acknowledgment of the subjective complaint of erectile inability by the patient (or patient and partner)
- Structured process that incorporates social clinical practice concepts to bring patients the best therapeutic outcomes

Clinical Practice Concepts

- Early detection
- Shared decision-making and treatment planning
- Role of partner interview
- Cardiac risk assessment
- Follow-up care

Detection

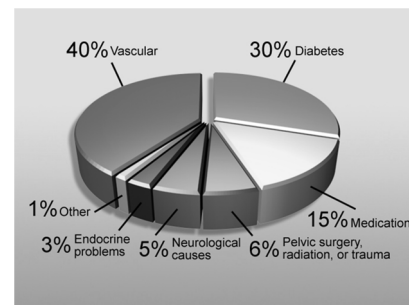
- Risk factor identification
- Screening high risk populations
- Diagnostic questionnaires

Use of Validated Questionnaires

For the man with ED, validated questionnaires are recommended to assess the severity of ED, to measure treatment effectiveness, and to guide future management. (Expert Opinion)

- eg, International Index of Erectile Function (IIEF), Erection Hardness (EHS), Sexual Health Inventory for Men (SHIM)
- Not valid for sexually inactive men

Organic Causes of ED: Percentage Distribution



With permission from Goldstein I, and the Working Group for the Study of Central Mechanisms in Erectile Dysfunction. Sci Am. August 2000;70-75.



Major Risk Factors for ED: Chronic Disease

Chronic Disease	~ED Risk Multiplied*
Diabetes ^{1,2}	4.1
Prostate disease ¹	2.9
Peripheral vascular disease ¹	2.6
Cardiac problems ¹	1.8
Hyperlipidemia ¹	1.7
Hypertension ^{1,2}	1.6

*Age-adjusted odds ratio.

1. Martin-Morales A et al. *J Urol*. 2001;166:569-575. 2. Braun M et al. *Int J Impot Res*. 2000;12:305-311.



Major Risk Factors for ED: Emotional Predictors*†

Emotional Predictor	~ED Risk Multiplied
Emotional problems/stress	3.6
General unhappiness	2.5
Dissatisfaction with partner	2.4
>20% decrease in income	2.1

*Compared with reference group without emotional factors.

†Based on National Health and Social Life Survey. (men, n=1410 [18-59 y])
Laumann EO et al. *JAMA*. 1999;281:537-544.



Major Risk Factors for ED: Emotional Predictors*

Emotional Predictor	~ED Risk Multiplied
Pessimistic attitude	3.9†
Depression	2.9†
Negative outlook on life	2.3†
Marital change	1.4
Employment change	1.4

*Based on the Massachusetts Male Aging Study. (N=1265)

†P<.05.

Reprinted from *Urologic Clinics of North America*, Volume 28, Rosen RC, Psychogenic erectile dysfunction: classification and management, pages 269-278, copyright 2001, with permission from Elsevier Science.



Major Risk Factors for ED: Lifestyle Issues

- Lack of exercise/sedentary lifestyle¹
- Obesity^{1,2}
- Heavy drinking¹
- Recreational drugs^{3,4}
- Smoking^{1,2}

1. Derby C et al. *Urology*. 2000;56:302-306. 2. Feldman HA et al. *Prev Med*. 2000;30:328-338. 3. Miller TA. *Am Fam Physician*. 2000;61:95-104, 109-110. 4. Jackson G et al. *Int J Clin Pract*. 1999;53:445-451.



Shared Decision-Making

- SDM is the cornerstone of patient-centered care
 - Sharing of information between patient and clinician is critical
- Clinician needs to be aware of
 - Health literacy of patient
 - Social, cultural, religious factors
- Panel strongly recommends involving a man's partner where possible and appropriate

Elwyn 2012, Epstein 2004, Hoffmann 2015, Hatzichristou 2010, Verulakonda 2008

Importance of Partner Interview*

- Partner interview shown to impact diagnosis and treatment 58% of the time^{1,2}
- Partner can provide important information¹⁻³
 - New perspective on sexual issues
 - Insight into quality of the relationship
 - Role in sexual dysfunction

*Partner interview may require a second visit.

1. Tiefer L, Schuetz-Mueller D. *Urol Clin North Am*. 1995;22:767-773. 2. Chun J, Carson CC III. *Urol Clin North Am*. 2001;28:249-258. 3. Tiefer L, Melman A. *Sex Disabil*. 1983;6:167-175.

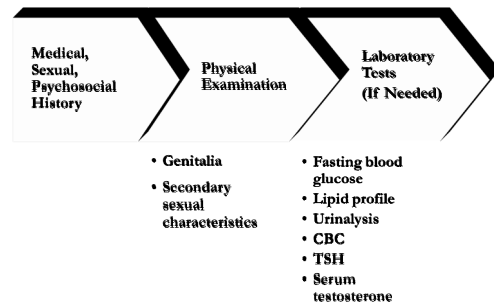


Cardiac Risk Assessment

- Recognition of the coexistence of ED and cardiovascular disease
 - Epidemiologic studies
 - Basic science research
- All ED patients require stratification of cardiovascular risk
 - High risk patients of unstable or refractory angina, recent history of myocardial infarction, certain arrhythmias, uncontrolled hypertension, should undergo cardiologic referral for cardiovascular stress testing and risk reduction therapy
 - Even low risk patients should receive minimum recommendations of cardiovascular disease management, e.g., lifestyle modifications, regular health monitoring

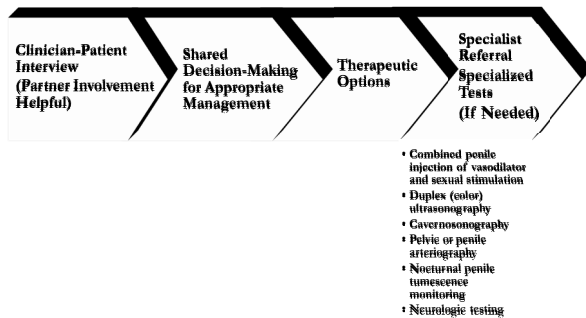
Kostis JB et al. Am J Cardiol 2005; 96:85M-93M.

Step-Care Approach to ED Management: Patient Identification and Assessment^{1,2}



1. Jardin A et al, eds. *Erectile Dysfunction*. Plymouth, UK: Health Publication, Ltd; 2000:117-138.
2. Recommendations of the 1st International Consultation on Erectile Dysfunction. In: Jardin A et al, eds. *Erectile Dysfunction*. Plymouth, UK: Health Publication, Ltd; 2000:711-726.

Step-Care Approach to ED Management: Clinician-Patient Dialogue^{1,2}

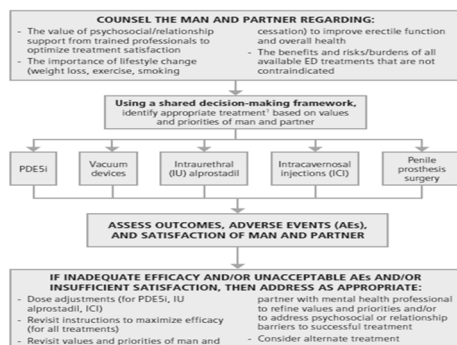


1. Jardin A et al, eds. *Erectile Dysfunction*. Plymouth, UK: Health Publication, Ltd; 2000:117-138.
2. Recommendations of the 1st International Consultation on Erectile Dysfunction. In: Jardin A et al, eds. *Erectile Dysfunction*. Plymouth, UK: Health Publication, Ltd; 2000:711-726.

Specialist Referral Indications

- Failure of initial treatment
- Younger patients with a history of pelvic or perineal trauma
- Patients with significant penile deformity
- Complicated endocrinopathies
- Complicated psychiatric or psychosexual disorders
- Need for vascular or neurosurgical intervention
- Medicolegal reasons

Treatment of ED



1. For men with testosterone deficiency, defined as the presence of symptoms and signs and a total testosterone <300 ng/dL, counseling should emphasize that restoration of testosterone levels to therapeutic levels is likely to increase efficacy of ED treatments other than prosthesis surgery.

Role of Mental Health Professional

For men being treated for ED, referral to a mental health professional should be considered to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship. (Moderate Recommendation; Evidence Level: Grade C)

- ED occurs in complex psychosocial context related to masculinity and sexuality
- Psychotherapy or psychosexual counseling may be helpful

Lifestyle Modifications for Comorbid Conditions

Clinicians should counsel men with ED who have comorbidities known to negatively affect erectile function that lifestyle modifications, including changes in diet and increased physical activity, improve overall health and may improve erectile function. (Moderate Recommendation; Evidence Level: Grade C)

- Metabolic conditions
- Cardiovascular conditions

PDE5i Availability

Men with ED should be informed regarding the treatment option of an FDA-approved oral phosphodiesterase type 5 inhibitor (PDE5i), including discussion of benefits and risks/burdens, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)

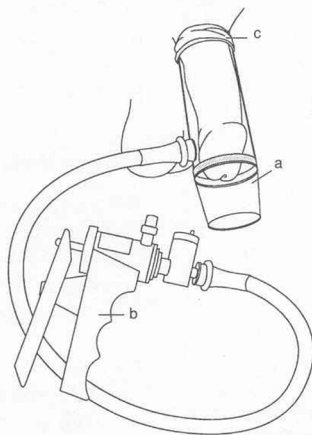
- In the US: sildenafil, tadalafil, vardenafil, and avanafil
- Effective in about 60% of men

Oral Pharmacotherapy: Type V PDE Inhibitors

- Mechanism of Action
 - “Augments” corporal smooth muscle relaxant effects
- Dosage/Administration
 - Lead time for gastrointestinal absorption
 - Presence of sexual stimulation
- Efficacy
 - 70% successful sexual intercourse rates
- Side Effects
 - Headaches, flushing, dyspepsia, nasal congestion, visual disturbances
- Contraindications
 - Nitrate therapy in any form
 - Alpha-blocker considerations

Vacuum Constriction Devices

- Mechanism
 - Negative pressure mechanically produces penile blood filling
- Dosage/Administration
 - Technical requirements
- Efficacy
 - Erection-like state: 67-90%
 - Satisfaction rates: 34-68%
- Side Effects (minor)
 - Genital ecchymosis, penile “pivoting”/coldness
- Contraindications
 - Sickle cell disease

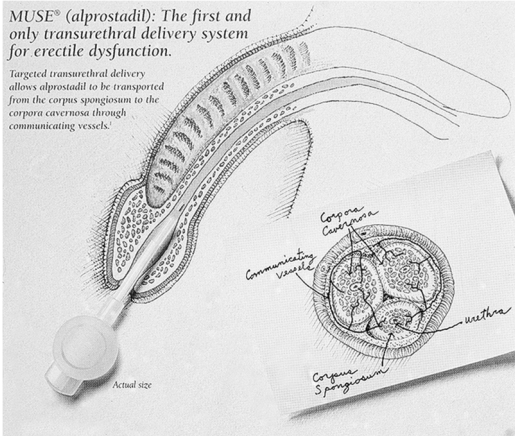


Intraurethral Pharmacotherapy: MUSE (Alprostadil)

- Mechanism of Action
 - Induces” corporal smooth muscle relaxant effects
- Dosage/Administration
 - Technical requirements
 - Proper dosing titration
- Efficacy
 - Responder rate: ~50%
- Side Effects
 - Local pain, urethral bleeding, dizziness, hypotension
- Contraindications
 - Men with priapism histories

MUSE® (alprostadil): The first and only transurethral delivery system for erectile dysfunction.

Targeted transurethral delivery allows alprostadil to be transported from the corpus spongiosum to the corpora cavernosa through communicating vessels.¹



Intracavernous Pharmacotherapy

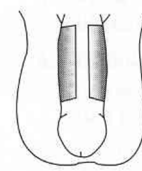
- **Mechanism of Action**
 - “Induces” corporal smooth muscle relaxant effects
- **Dosage/Administration**
 - Technical requirements
 - Proper dosing titration
- **Side Effects**
 - Penile pain, penile fibrosis, priapism
- **Contraindications**
 - Men with priapism or severe coagulopathy histories

Intracavernous Pharmacotherapies

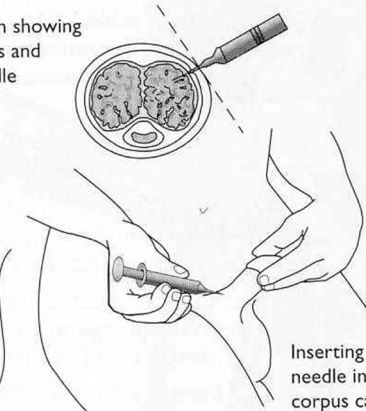
Trade Name	Drug	Dosages	Efficacy (intercourse)
Caverject	Alprostadil (Prostin VR)	5-40 ug/ml	~70%
Edex	Alprostadil (Prostin VR)	5-40 ug/ml	~70%
Bi-mix	Alprostadil + Pheentolamine	20 ug/ml + 0.5 mg/ml	~90%
Binix Androskat (EU)	Papaverine + Pheentolamine	30 mg/ml + 0.5 mg/ml	~90%
Tri-mix	Alprostadil + Papaverine + Pheentolamine	10 ug/ml + 30 mg/ml + 1.0 mg/ml	~90%
Invicorp	VIP + Pheentolamine	NA	~80%
Thymoxamine	Moxisylyte	NA	~70%

Cross-section showing injection sites and angle of needle insertion

Injection sites along the side of the penis

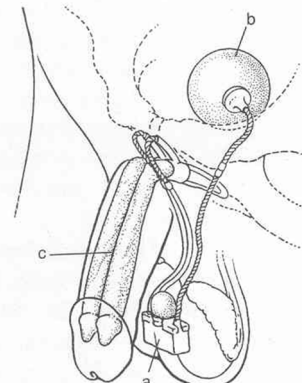


Inserting the needle into the corpus cavernosum at the injection site



Penile Prosthesis Surgery

- **Indications**
 - Major penile injury or deformity
 - When medical therapy is contraindicated, unsuccessful, or undesirable
- **Mechanism of Action**
 - “Splint” within the penis produces rigidity
- **Technique**
 - Hand dexterity
- **Side Effects**
 - Risk of infection or device malfunction
- **Contraindications**
 - Surgical candidacy considerations



Penile Vascular Surgery

- **Arterial Revascularization**
 - Considered to address arteriogenic ED
 - Indications: age less than 55 years, non-smoker, non-diabetic, absence of venous leakage, radiographic confirmation of stenosis of the internal pudendal artery
 - Options: inferior epigastric artery input to dorsal artery or vein
- **Venous Reconstruction**
 - Proposed to correct veno-occlusive ED
 - Presently considered investigational
 - Owing to inaccurate or deficient methods for diagnosing and correcting the relevant defect

Follow-Up Issues

- Reassessment of medical and psychosocial conditions
- Evaluation of potential adverse drug reactions or drug interaction effects
- Evaluation of the need for dosage titration or treatment substitution
- Attention to patient responses to therapy and satisfaction

Expected Developments in the Near Future

- **New pharmacologies**
 - Guided by pathophysiology
- **New surgery techniques**
 - Tissue transplants
- **New devices**

Key Points

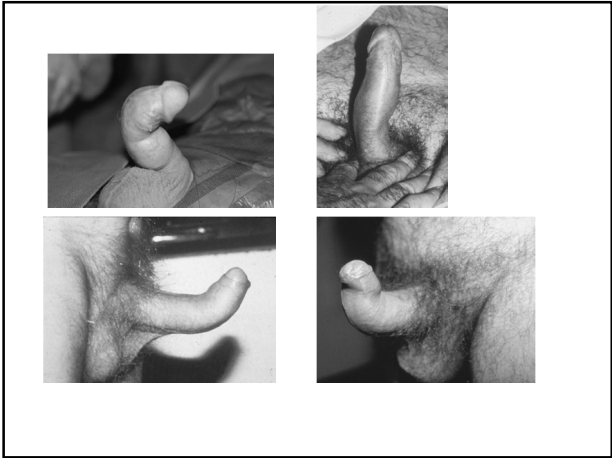
- Approximately 20% of adult men worldwide experience ED.
- The basic evaluation of ED consists of a detailed case history, physical examination, and proper laboratory tests.
- An informed decision-making process that combines goals and preferences of the patient (and partner) and balanced and thorough guidance of the clinician should dictate the best therapeutic outcome.

Comprehensive Review of Urology:	
Peyronie's Disease and Priapism	
Hossein Sadeghi-Nejad, MD, FACS	
<i>Professor of Surgery in Urology Rutgers– New Jersey Medical School Hackensack University Medical Center Chief of Urology, VA NJ Health Care System</i>	
	

Financial Disclosures	
None	
	

Peyronie's Disease	
American Urological Association (AUA) Guideline	
PEYRONIE'S DISEASE: AUA GUIDELINE	
Ajay Nehra, Ralph Alterowitz, Daniel J. Culkin, Martha M. Faraday, Lawrence S. Hakim, Joel J. Heidelbaugh, Mohit Khera, Kevin T. McVary, Martin M. Miner, Christian J. Nelson, Hossein Sadeghi-Nejad, Allen D. Seftel, Alan W. Shindell, and Arthur L. Burnett	
THE JOURNAL OF SEXUAL MEDICINE	
Evidence-Based Management Guidelines on Peyronie's Disease	
Eric Chung, FRACS,^{1,2} David Ralph, FRCS,³ Ates Kagioglu, MD,⁴ Guillo Garaffa, FRCS,⁵ Ahmed Shamsodini, MD,⁵ Trinity Bivalacqua, MD,⁶ Sidney Glina, MD,⁷ Lawrence Hakim, MD,⁸ Hossein Sadeghi-Nejad, MD,⁹ and Gregory Broderick, MD¹⁰	
	

PEYRONIE'S DISEASE DEFINITION	
<i>...An acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, deformity, erectile dysfunction, and/or distress...</i>	
American Urological Association (AUA) Guideline	
PEYRONIE'S DISEASE: AUA GUIDELINE	
Ajay Nehra, FRACS,^{1,2} David Ralph, FRCS,³ Ates Kagioglu, MD,⁴ Guillo Garaffa, FRCS,⁵ Ahmed Shamsodini, MD,⁵ Trinity Bivalacqua, MD,⁶ Sidney Glina, MD,⁷ Lawrence Hakim, MD,⁸ Hossein Sadeghi-Nejad, MD,⁹ and Gregory Broderick, MD¹⁰	



EPIDEMIOLOGY	
Schwarzer (2001; BJU) community-based; Cologne, Germany	
➤ Prevalence 3.2% in men aged 31-78 years ➤ 7.1% among men aged 50-69 years	
El-Sakka (2006 Eur Ur):	
➤ Prevalence 7.9% among men with ED	

Prevalence of Peyronie's Disease: 8,000-Man Survey

■ Clinical complaints:

– Angulation	119/142	(84%)
– Painful erections	66/142	(46%)
– Erectile dysfunction	58/142	(40.8%)
– Combination	46/4432	(1.03%)

U. Schwarzer et al., J Urol 2000.

PATHOPHYSIOLOGY

- Acquired inflammatory disorder of the tunica albuginea
- Microvascular trauma to the penile shaft associated with penile buckling in the erect or semi-erect state secondary to sexual activity
- Many patients do not recall an incident that preceded symptom onset

SYMPTOMS

- Disorganized, excessive deposition of collagen → formation of plaque within the penile tunica albuginea
- penile curvature, deformity, and pain
- Erectile dysfunction common
- Emotional and psychosocial consequences are significant

ACTIVE VS STABLE DISEASE

➤ Treatment depends on active vs. stable symptoms

Active disease- dynamic and changing symptoms

- Penile and/or glanular pain/ discomfort with or without erection

Stable disease- *Symptoms* unchanged for at least three months

- Pain with or without erection may be present (less common)
- Curvature may be uniplanar or biplanar and may not be dependent on the size and magnitude of the plaque

Natural History Peyronie's Disease

- 12% improve
- 40% remain stable
- 48% worsen

Mulhall et al, J Urol 2006; 175: 2115

Typical active phase 12-18 mo

➤ Significant number will progress

GUIDELINE STATEMENT 5

The clinician may offer oral non-steroidal anti-inflammatory medications to the patient suffering from active Peyronie's disease who is in need of pain management (*Expert Opinion*)

GUIDELINE STATEMENT 6

Clinicians should not offer oral therapy with vitamin E, tamoxifen, procabazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine.

[Moderate Recommendation; Evidence Strength Grade B(vitamin E)/ B(omega-3 fatty acids)/ B (Vitamin E + propionyl-L-carnitine)/C(tamoxifen)/ C(procabazine)]

GUIDELINE STATEMENT 7

Clinicians should not offer electromotive therapy with verapamil. *(Moderate Recommendation; Evidence Strength Grade C)*

GUIDELINE STATEMENT 8

Clinicians may administer intralesional collagenase clostridium histolyticum combination with modeling by the clinician and by the patient for the reduction of penile curvature in patients with stable Peyronie's disease, penile curvature $>30^\circ$ and $<90^\circ$, and intact erectile function (with or without the use of medications). (Moderate Recommendation; Evidence Strength Grade B)

Clinical Efficacy, Safety and Tolerability of Collagenase Clostridium Histolyticum for the Treatment of Peyronie Disease in 2 Large Double-Blind, Randomized, Placebo Controlled Phase 3 Studies

Martin Gelbard,*† Irwin Goldstein,‡ Wayne J. G. Hellstrom,§ Chris G. McMahon,‡ Ted Smith,‡ James Tursi,‡ Nigel Jones,‡ Gregory J. Kaufman‡ and Culley C. Carson III‡

- Two Multicenter Randomized, Double Blind, Placebo Controlled Studies
- USA and Australia (IMPRESS I & II)
- **Primary end points**
 - Improvement (%) from baseline penile curvature
 - Change from baseline in PD symptom bother (PDQ)

THE JOURNAL OF UROLOGY®

Vol. 190, 199-207, July 2013

IMPRESS I and II – Intralesional Collagenase Plus Modeling

- The definitive trials that lead to FDA approval
- Up to 8 injections of 10,000 U over 24 weeks
- Clinician modeled the penis after each cycle
- Patients were instructed to model at home 3 x day
- Follow up 7.5 months
- Exclusion criteria more extensive than 2012 trial:
 - Curvature $<30^\circ$ or $>90^\circ$
 - Isolated hourglass deformity without curvature
 - Calcified plaque or curvature proximal to base
 - ED unresponsive to PDE5 inhibitors
 - Lack of PGE1 erection during measurement

IMPRESS I and II- Intralesional Collagenase Plus Modeling

Subgroup	Change from baseline curvature	% change from baseline curvature
Collagenase + modeling (n=202)	-17.0°	33% reduction
Placebo + modeling (n=107)	-9.3°	18.2% reduction

Co-primary endpoint result Erectile curvature improvement from baseline to week 52



33% change from baseline represented in the images

➤ Men with lesser degrees of deformity may have similar bother domain scores as those with more severe curvature deformity

<https://peyronies-disease.xiaflex.com/hcp/clinical-data>

GUIDELINE STATEMENT 8 Considerations

Body of evidence strength is Grade B

Expected average curvature reduction is 17 degrees

Average difference between collagenase and placebo was statistically significant but only 7.7°

IIEF overall satisfaction improvement by one point

BJUI
BJU International

Sexual Medicine

Analysis of the clinical safety of intralesional injection of collagenase *Clostridium histolyticum* (CCH) for adults with Peyronie's disease (PD)

Culley C, Carson III, Hossein Sadeghi-Nejad*, James P. Tursi†, Ted M. Smith†, Gregory J. Kaufman†, Kimberly Gilbert† and Stanton C. Honig*

BJU Int 2015; 116: 815-822

GUIDELINE STATEMENT 9

Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional collagenase regarding potential occurrence of adverse events, including penile ecchymosis, swelling, pain, and corporal rupture. (Clinical Principle)

GUIDELINE STATEMENT 10

Clinicians may administer intralesional interferon α -2b to patients with Peyronie's disease. (Moderate Recommendation; Evidence Strength Grade C)

Injection Technique

Local (over injection site) or penile nerve block

- Multiple punctures (25-27 g. needle) into the plaque → widely distribute drug
- 6-10 cc of mixed solution per session q 2 wks: 6-12 plaque injections total



Intralesional Interferon α -2b Trial

- Evaluated the use of intralesional IFN α -2b
- Average PD symptoms >12mo
- 5 MU of IFN α -2b q 2 weeks for 12 weeks
 - (Note: many studies use 2MU in 10cc)
- Curvature, plaque size, penile pain, erectile function and penile hemodynamics were measured at baseline and study completion
- Inclusion criteria
 - Curvature >30°
- Exclusion criteria
 - Calcified plaques

Interferon α-2b

Subgroup	Change from baseline curvature	% patients with resolution of pain	Decrease in size of plaque
IFN α-2b (n=50)	-13.5°	67.7%	2.6 cm²
Placebo (n=53)	- 4.5°	28.1%	0.9 cm ²

IFN α-2b: significant improvement in outcomes except EF
Significant improvement in PSV and mean resistive index

- Proportion of men with normal vascular status increased significantly in IFN group (31.5% to 57.8%) but not in placebo

➤ **9° difference vs placebo**

Interferon α-2b Considerations for Patient Counseling

Body of evidence strength is Grade C.
Expected average curvature reduction: 13.5°
Average difference with placebo: 9 degrees

Despite modest curvature reduction, consider reduction in other PD outcomes (plaque size, pain, vascular outcome)

GUIDELINE STATEMENT 11

Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional interferon α-2b about potential adverse events, including sinusitis, flu-like symptoms, and minor penile swelling. (*Clinical Principle*)

40-100% with AEs. Effectively managed with OTC NSAIDs; Duration of AEs typically 48 hours or less

GUIDELINE STATEMENT 12

Clinicians may offer intralesional verapamil for the treatment of patients with Peyronie's disease. (*Conditional Recommendation; Evidence Strength Grade C*)

Note: Dose is typically 10 mg / 10 cc

Randomized Controlled Trials: Intralesional Verapamil

Rehman Trial	Shirazi Trial
- Mean disease duration of 16 months - Baseline mean curvature of 37.7° in verapamil group, 33.6° in placebo 10-27 mg administered weekly for 6 months - Reported significant decrease in plaque length, width, and volume in verapamil group but not in the placebo group	- Mean disease duration of 21.3 months - Baseline mean curvature of 49.7° in verapamil group, 45.6° in placebo - 10 mg administered twice weekly for 3 months - Reported similar decrease in plaque length, width, and volume in both groups

Intralesional Verapamil

- Body of evidence strength is Grade C based on conflicting findings from the RCT trials.
- Lack of control for natural PD course increases the uncertainty of the results
- Clinicians should be aware that the balance between benefits and risks is unclear.

Cost considerations not addressed by the AUA panel
Potential advantage for some patients

Verapamil Adverse Events

Penile bruising, dizziness, nausea, and pain at the injection site.

Generally very mild in nature

Shock Wave Therapy

Do not use for the reduction of penile curvature or plaque size.

ESWT may be used to improve penile pain

(AUA-G Conditional Recommendation; Evidence Strength Grade B)



Surgical Approaches

1. *Tunical Shortening Procedure* – Reconstructive procedures on convex side (opposite to the plaque)
2. *Penile Lengthening Procedure* – Reconstructive procedure on concave side (same side as plaque)
- incision/excision & grafting
3. *Penile Prosthesis* (manual modeling, tunical incision/excision ± grafting)

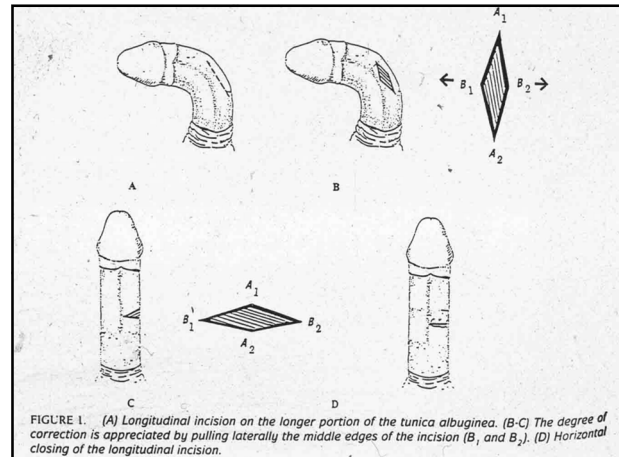
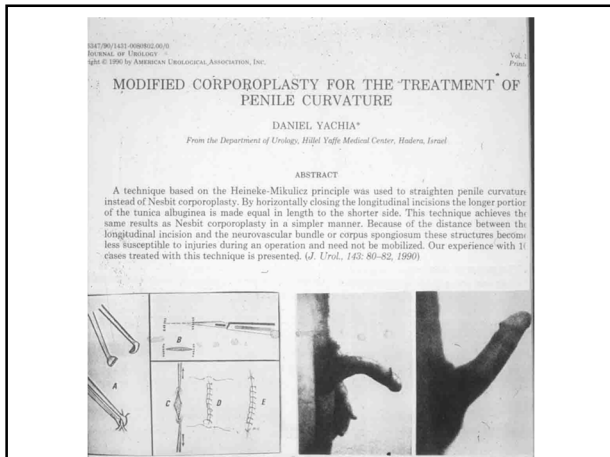
Tunical Shortening Procedures

Nesbit Procedure (1965) – initially described for correction of congenital abnormalities of penis

- Pryor (1985) applied technique to Peyronie's deformities
- Technique – circumcision incision, artificial erection, ellipse(s) excised – 1 mm for every 10° curvature
- Results – simple, safe, 80% success rate
- Drawbacks – Penile shortening (13-37%), urethral injury, glans numbness, hematoma, ED

Tunical Shortening Procedures

- Modified Nesbit Procedure (Lemberger 1984, Yachia 1990)
- Allis clamps used to straighten penis with artificial erection, longitudinal incision, closed horizontally (Heineke-Milkulicz principle)
- Results – 90% successful straightening, 95% preservation of erections, 80% satisfaction
- Drawback – Penile shortening in 67%

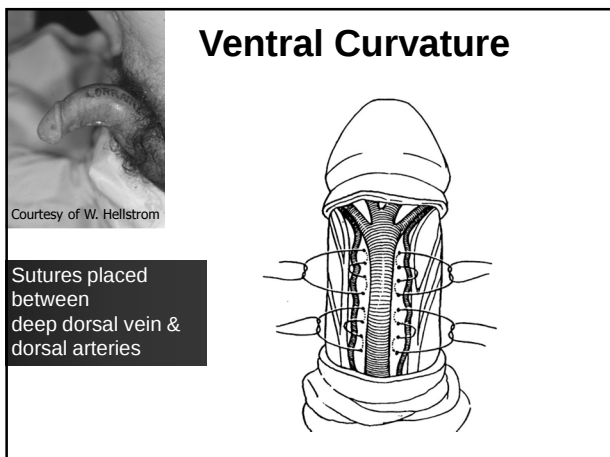
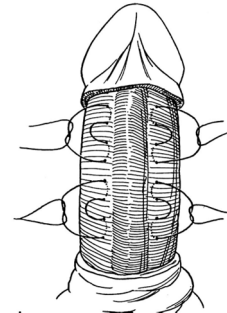
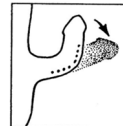


Tunical Shortening Procedures

Plication Procedures

- No excision or incision
- Non-absorbable sutures (2-0 Ticron, Prolene, Tevdek) placed on opposite side to curvature and knots buried
- 2-3 pairs of sutures usually used
- Results: Success 40-100%
- Drawbacks – Recurrence of curvature, penile pain and shortening

Dorsal Curvature



Tunical Lengthening Procedures

- Indications: Severe curvatures, marked penile shortening (or short penis), deformation, or waisting
- Incision/excision of plaque and graft placement
- Drawbacks – Sensory deficit, urethral injury, residual /recurrent curvature, **ED**

Grafting Materials

- Autografts
 - e.g.: dermis, dura mater, tunica vaginalis, dorsal penile or saphenous vein, temporalis fascia, crura, fascia lata, etc.
- Synthetic Inert Substances
 - e.g.: Dacron, Gortex, silicone with silastic borders
- Allografts or Xenografts
 - Human cadaveric pericardium (ie Tutoplast, Coloplast, Denmark)
 - SIS (porcine small intestinal submucosa) (Cook, Indianapolis, IN)

Excision and Grafting

- Buck's fascia entered just lateral to the urethra
- Dissect the neurovascular bundle free for dorsal plaques and the urethra for ventral plaques.
- Alternatively, dorsal approach by removing the dorsal vein and dissecting neurovascular bundle off laterally to expose plaque

Slide courtesy of Laurence Levine

Incision/Partial Excision & Grafting - Indications

- Surgical Algorithms & Guidelines agree x 20y
- **Must have strong pre-op erections !!!**
- Curvature > 60 degrees
- Significant shaft narrowing
- Hinge-effect present
- Extensive plaque calcification

N.B. – Plaque and deformity stable & coitus compromised 2° deformity

Ralph et al JSM 2010;
Chung et al 2016

Advantages of PIG/PEG Procedure

- Best opportunity to correct severe curvature > 60-70°
- Only approach to reestablish girth & correct hinge
- Least likely to cause further length loss
- Most likely to enhance length with or without traction post-op

Severe Curve 85° w/ Indent and Hinge



Courtesy of L. Levine, M.D.

Caliber & Curve Corrected



Courtesy of L. Levine, M.D.

Complications of Grafting

- Hematoma
- Wound infection
- Urinary retention or urethral injury
- Distal sensory deficit/numbness of glans (neuropria)
- Diminished distal rigidity (venous leak ?)
- Graft contraction
- Erectile dysfunction

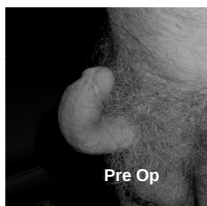
Inflatable Penile Prosthesis

Indications: PD & ED

- Malleable: poor long-term satisfaction (Montorsi, J Urol 1993)
- Inflatable: (AMS-CX or Coloplast Titan best; Never AMS-Ultrex; LGX NOT recommended)
- Possible AEs– infection, urethral injury, distal sensory deficit, prosthesis failure, penile shortening

Wilson SK, Delk JR: J Urol 152:1121, 1994
Montague DK et al: J Urol 156:1633, 1996

Patient with curvature > 70°



- > 40%: corrected with implant alone
- 30° or less → no adjunctive measures
- Hourglass deformity: corrects with time
- Inflated cylinders act as a tissue expander
- With usage after 1 yr → straight & symmetrical



Protect pump with clamps

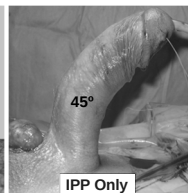
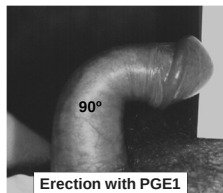


Protect corporotomies

Insert & inflate IPP to maximum
Bend penis in opposite direction firmly
Hold pressure for 90 seconds
Remove clamps & inflate again (2 or 3 pumps)

Wilson, Delk: J Urol 165:825, 2001

Modeling Procedure



Reprotect & repeat modeling
After 2 modeling sessions, deflate completely
Pull on strings & only inflate 75%
Then judge results — quit if <30°

IPP + Modeling Procedure

- Urethral Injury: 4%
- Corporal Rupture: 2%
- AMS CX or Coloplast Titan
- AMS LGX not recommended

Wilson SK, Delk JR: J Urol 152:1121, 1994
Montague DK et al: J Urol 156:1633, 1996

Take Home Messages Medical Therapies

- ~ 5% of the population affected
- Heterogeneous presentation
- Individualized Treatment
 - Review of AEs, costs, comorbidities
- Modeling is critical in collagenase Rx
- Not optimal for patients with PD and ED unresponsive to PDE5-Is

Take Home Messages Surgical Therapies

- Many will need surgery
 - Gold standard for definitive correction
 - Penile plication procedures are generally safe with an easier learning curve
 - Provide excellent results (92-99% curve improvement or resolution) with minimal morbidity
 - Excision grafting considered for severe cases
 - IPP and modeling for PD + ED combination



Priapism Update

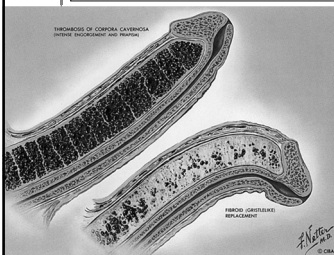
Hossein Sadeghi-Nejad, MD, FACS

Professor of Surgery in Urology
Rutgers– New Jersey Medical School
Hackensack University Medical Center
Chief of Urology, VA NJ Health Care System



Priapism Definition:

Pathological condition of a penile erection - persists beyond or unrelated to sexual interest or stimulation



4
hours

Sadeghi-Nejad H and Seftel A
Current Urology Reports 2002, 3:492-498

AFUD Thought Leader Panel, IJIR 5:S39, 2001

Classification

- Ischemic
 - Veno-occlusive or low flow. Nonsexual persistent erection with little or no cavernous blood flow . Corpora is rigid and tender to touch
- Non-ischemic
 - Arterial or high flow. Nonsexual persistent erection with unregulated cavernous arterial inflow. Phallus is neither fully rigid nor painful
- Stuttering
 - Ischemic priapism with intervening periods of detumescence

Classification

- Ischemic (veno-occlusive” or “low flow”)
 - Most common variant (~ 95% of cases)
 - Trapping of mixed venous blood
 - ischemia & pressure → pain & rigidity
- Very high ED rates (~ 90%) if > 24 hrs

TRUE EMERGENCY

Pryor, J. and Hehir, M. (1982) *Br J Urol*

Classification

- Non-ischemic (“high flow” or “arterial”)
 - Elevated vascular flow through corpora
 - Penile/perineal trauma
 - Corpora cavernosa not fully rigid or painful
 - No hypoxia / acidosis on blood gas sampling

High Flow Priapism - Etiology

Table 2 Etiology of the 202 cases of high-flow priapism reported in the literature.^a

Etiology	Percentage of cases
Traumatic/isotrogenic laceration of a penile artery	70.5
Blunt penile trauma	3.8
Blunt perineal trauma	40.4
Straddle trauma	24.4
Cavernosography	0.6
Penile revascularization	1.3
Malignant arrosion of penile vessels	4.5
Inherited disease (sickle cell anemia, FABRY'S DISEASE)	5.8
Drug abuse and intracavernous injection of prostaglandin E1	2.5
Unknown	16.7

^aTable compiled using data presented by Kuefer and associates.²

Bochinski DJ *et al.* (2004) Erectile dysfunction and priapism.
Nat Clin Pract Urol 11: 49–53 doi:10.1038/ncpuro0022

Classification Other categories

- Recurrent (Stuttering) Priapism
 - Recurring ischemic attacks, often sickle cell patients
- Refractory Priapism
 - Immediately recurrent nonischemic erectile state following aspiration/incision of the corpora for ischemic priapism
 - Veno-occlusive priapism can convert to non-ischemic priapism
- Neurogenic Priapism
 - Central/Peripheral nervous dysregulation
- Idiopathic
- Drug Induced

Epidemiology

- 1.5 per 100,000 person years
 - 2.9 if > 40 years old
- Much higher in “at risk” population
- 42% - 64% prevalence in SCD
- Sickle β -Thal → 89% probability age 20

Eland *et al*; *Urology*, 2001, 57 (5): 970-2
Mantadakis *et al.*; *J Ped Hemat Onc*, 1999; 21: 518-22

Incidence of Priapism in Emergency Departments in the United States

Florian Roghmann,^{*,†,‡} Andreas Becker,^{†,‡} Jesse D. Sammon,[†] Miriam Ouerghi,[†] Maxine Sun,[†] Shyam Sukumar,[†] Orchidee Djahangirian,[†] Kevin C. Zorn,[§] Khurshid R. Ghani,[†] Giorgio Gandaglia,[†] Mani Menon,[†] Pierre Karakiewicz,[†] Joachim Noldust and Quoc-Dien Trinh[†]

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- 5.34 per 100,000 males per year
- 31.4% increase in summer months
- 13.3% result in hospitalization
- Predictors of admission: comorbidity profile, insurance, hospital location, emergency dept volume

Natural History

- Ischemic Priapism
 - Pryor 2004- reported 90% of men with ischemic priapism lasting 24 hours fail to regain ability to perform sexual intercourse
 - Montague 2003- ED rate of 35% in pts treated systemically with no direct relief of ischemia
- Non-ischemic Priapism
 - Generally have preservation of erectile function
 - 62% spontaneously resolve

Pathophysiology - Ischemic

- Irreversible effects - combination of hypoxia, acidosis and glucopenia at 4 hours
- Reperfusion injury after ischemic priapism resolution
- 12 hours- Trabecular interstitial edema
- 24 hours- sinusoidal endothelium is denuded
- 48 hours- smooth muscle cells undergo necrosis or become transformed into fibroblast like cells

Pathophysiology - Non-ischemic

- Traumatic disruption of penile vasculature → unregulated blood entry
- Fistula formation between cavernous artery and lacunar spaces → blood bypasses the helicine arteriolar bed

Diagnosis

- Unique / “obvious” presentation
- H&P – Differentiating factors
 - Pain? Duration? Glans involved?
 - Antecedent factors? Prior episodes/successful Rx? Predisposing conditions? Sickie crisis in SCD?



Lab tests should not delay prompt Rx

Ischemic vs Non-ischemic

EVALUATION	
Duration	
Degree of pain	
Prior h/o Prx and tx	
Anti-HTN, anticoagulants	
Anti-depressants and psychoactive	
Alcohol	
Cocaine, marijuana	
Intracavernous injections	
Sickle cell disease	
Ischemic – full rigidity, tender	
Non-ischemic – partial rigidity, non-tender	
CBC, Reticulocyte count	
Electrophoresis for SCA, thalassemias	
Sicklelex in acute setting	
Urine tox + Cav. blood gas	
pO2 < 30, pCO2 > 60, pH < 7.25	

Diagnosis

- CBC / wbc diff, Plt, urine toxicology, Reticulocyte count & hgb electrophoresis (SCD trait & hemoglobinopathies)
- Direct aspiration of corporal blood

Typical Blood Gas Values

Source	PO ₂ (mmHg)	PCO ₂ (mmHg)	pH
Ischemic priapism	< 30	> 60	< 7.25
Normal ABG	> 90	< 40	7.40
Normal Mixed VBG	40	50	7.35

Penile blood gas sampling



Diagnosis: Radiologic Evaluation

Color Doppler Ultrasound

Lithotomy or frog-leg position

- **Ischemic:** minimal to absent flow in cavernosal arteries / within corpora
- **Nonischemic:** normal to high flow
 - Fistula; Pseudoaneurysm

MRI: Unusual pathologies. Diagnose nonviable tissue. (access, cost, delay)

Treatment Goals

- Detumescence
- Preservation of erectile function
- Diagnosis of etiology

Treatment Ischemic Priapism

- Stepwise + timely / aggressive
 - nerve block
- Aspiration
- Irrigation when necessary
- Injection of alpha agents

Treatment of Ischemic Priapism

➤ Concurrently treat the underlying disease and emergent condition

➤ Treatment proceeds in a stepwise fashion

➤ Surgical shunts should be considered only after injection treatment has failed

➤ Intercavernosal injection of phenylephrine rarely successful if priapism present for > 48hrs

No fixed set of rules or a definition of legal standard of care

AUA Guidelines on Priapism, 2003

Penile aspiration and Irrigation

18 gauge proximal needle insertion

Transglanular angiocath aspiration also an option



First shot is the best shot

Treatment – Ischemic Priapism

- Corporal aspiration relieves the compartment syndrome
- Counteracts local acidotic and anoxic metabolic derangements

Bivalacqua and Burnett, Urology 2006

- Sympathomimetic agent
 - Better resolution of priapism; less ED

AUA Guidelines, Montague et al. J Urol, 2003

Sympathomimetic Agents

Phenylephrine

- Preferred agent based on selectivity (no signif. β effect)
- α_1 agonist.
- 100-200 μ q 5-10 min
- Monitor BP

Ischemic Priapism Rx

- Repeated aspirations & phenylephrine injections as needed
- Should be done before operating
- 48-72 hours: unlikely to resolve with intracavernous treatment

May require surgical shunting

Distal Shunts

CORPORAL-GLANDULAR

First choice
Easiest to perform
Fewest complication rates
Winter Shunt (66% success) - large biopsy needle
Ebbehøj (73% success) - scalpel



Ebbehøj shunt



	Distal Shunts CORPORAL-GLANDULAR
	Al-Ghorab Excision of piece of tunica albuginea at tip of corpus cavernosum <u>Most effective</u>, can be attempted if other two fail Usually close spontaneously with time Long term patency leads to ED 74% success
	

	Proximal Shunts PROXIMAL
	Warranted if distal shunts fail More time consuming and technically challenging <u>50% ED</u> vs. 25% with distal shunts
	<u>Quackels</u> Shunt between corpora cavernosum and spongiosum 77% resolution
	<u>Grayhack</u> Shunt between corpora cavernosum and saphenous vein 76% resolution

	Treatment Non-Ischemic Priapism
	➤ Different approach altogether ➤ Initial Rx is OBSERVATION! ➤ Aspiration is only diagnostic

	Treatment of Non-ischemic Priapism
INITIAL MANAGEMENT	➤ Observation ➤ Ice and site-specific compression ➤ Immediate embolization can be performed - should be counseled re. risk of ED ➤ <u>Chance of spontaneous resolution</u> ➤ Lack of significant consequences expected from delaying
SECONDARY MANAGEMENT	➤ Corporal aspiration is of diagnostic value only ➤ Selective arterial embolization Second line tx for failed observation ➤ 78% success and 38% ED with permanent agents ➤ 74% success & 5% ED with temporary embolization (Autologous clot and absorbable gels)

	Treatment Non-Ischemic Priapism
	Embolization possible AEs: • ED (up to 50%) • Penile gangrene • gluteal ischemia • Purulent cavernositis • Perineal abscess

	Treatment Non-Ischemic Priapism
	➤ Androgen blockade ➤ Luprolide, Ketoconazole, Bicalutamide ➤ Small study (n=7) ➤ AEs (decreased libido, fatigue) ➤ 6 out of 7 improved ➤ ? Natural progression vs Rx Mwamukonda, K. Et al., (2010) <i>J Sex Med</i>

Recurrent Priapism

- RIP or “stuttering”
- Uncommon; Often sleep related
- Typically less than 3-4 hours
- 28% progress to ischemic priapism
- Possible progression to corporal fibrosis and ED

Morrison BF and Burnett AL, Curr Urol Report; 2012
Montague et al, AUA Guidelines, J Urol 2003

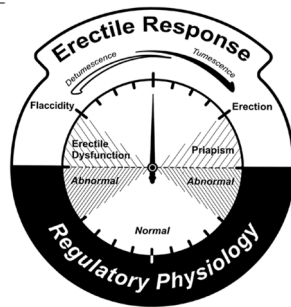
Recurrent Priapism

- SCD most common cause
 - 72% with priapism have RIP episodes
- Idiopathic and neurological causes
- History of prolonged (> 4 hr) priapism episode may predispose to RIP

Adeyoku et al; BJU Int 2002; 90: 898-902
Broderick and Harkaway; IJIR; 1994; 6: 9-16

Recurrent Priapism Pathophysiology

Phosphodiesterase
-5A dysregulation in
penile erectile
tissue is a
mechanism of
priapism



Hunter C, Champion, Trinity J, Bivalacqua,
Eiki Takimoto, David A. Kass, Arthur L. Burnett
Proc Natl Acad Sci 102(5), 1661-6, 2005

Recurrent Priapism Pathophysiology

- Penile endothelial NO deficiency
- → cGMP-dependent protein kinase down regulation
- → PDE5 dysregulation
- Poor corp. smooth muscle tone control
- Prolonged erection with stimuli

Sauzeau et al; J Biol Chem 2003; 278: 9472-80
Champion et al; Proc Natl Acad Sci 2005; 102: 1661-6

Recurrent Priapism Treatment

- Prevent future episodes
- Acute Rx: aspiration & α -agonists
- Hormonal manipulation
 - GnRH agonists, antagonists
 - Antiandrogens, estrogens
 - 5ARIs
 - Ketoconazole
- Duration of treatment ???
- Caution in the younger population

Recurrent Priapism Treatment

- Oral α -agonists
- Digoxin
- Terbutaline
- Gabapentin
- Baclofen

Gupta et al; J Urol; 1998; 159: 1529-36
Sadeghi-Nejad et al; J Urol 1997; 157:202
Priyadarshi S. IJIR; 2004; 16: 424-6

Recurrent Priapism Treatment

EUROPEAN UROLOGY 65 (2014) 480–489

Table 9 – Recommendations on the treatment of stuttering priapism

Recommendation	GR
The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can generally be achieved pharmacologically. The management of each acute episode is similar to that for ischaemic priapism.	B
Hormonal therapies (mainly gonadotropin-releasing hormone agonists or antagonists) and/or antiandrogens may be used for the prevention of future episodes. They should not be used before sexual maturation is reached.	C
Phosphodiesterase type 5 inhibitors have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism. Treatment should be initiated only when the penis is in its flaccid state.	C
Other systemic drugs (digoxin, α -adrenergic agonists, halofenate, gabapentin, terbutaline) can be considered, but data are even more limited. Intracavernosal self-injections at home of sympathomimetic drugs can be considered for the treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	C

GR = grade of recommendation.

PDE5-I & Recurrent Priapism

N= Thirteen patients SCD

- Priapism recurrences min 2x/week
- Sildenafil 50 mg or placebo daily, unassociated with sleep or sexual activity, for 8 weeks
- Followed by open-label use of this regimen for an additional 8 weeks.

THE AMERICAN JOURNAL OF MEDICINE
Randomized Controlled Trial of Sildenafil for Preventing Recurrent Ischemic Priapism in Sickle Cell Disease

Arthur L. Burnett, MD, MBA, Uzoma A. Aniele, MD, Irene N. Trueheart, RN, John J. Strouse, MD, PhD, James F. Casella, MD

Received: March 5, 2014; Received in revised form: March 13, 2014; Accepted: March 13, 2014; Published Online: March 25, 2014

PDE5-I & Recurrent Priapism

- Major priapism episodes were decreased 4-fold in patients monitored "on-treatment."
- Sildenafil systematic dosing as strategy to prevent recurrent ischemic priapism in SCD

Burnett et al, Am J Med; March 2014 epub

Prevention of Recurrent Ischemic Priapism with Ketoconazole: Evolution of a Treatment Protocol and Patient Outcomes

Michael P. Hoeh, MD and Laurence A. Levine, MD
Department of Urology, Rush University Medical Center, Chicago, IL, USA

- Retrospective chart review and phone survey of 17 patients with RIP
- Primary outcome: RIP prevention KTZ
- Daily prolonged erections pre-Rx
- ER visit per pt prior to Rx = 6.5

DOSE: 200 TID + Prednisone 5.0 mg 2 wks,
→ KTZ 200 qhs 6 months

Prevention of Recurrent Ischemic Priapism with Ketoconazole: Evolution of a Treatment Protocol and Patient Outcomes

Michael P. Hoeh, MD and Laurence A. Levine, MD
Department of Urology, Rush University Medical Center, Chicago, IL, USA

- RESULTS:
 - No pt had ER visits for priapism on KTZ
 - 16 / 17 (94%) complete resolution
 - Effective immediately after starting Rx
 - No reported sexual AEs due to KTZ
 - 1 pt stopped due to nausea / vomiting
 - 14 / 16 discontinued after median 7 mo
 - 29 % no recurrence;
 - 78.6% partial or total resolution

Hoeh M and Levine L: J Sex Med, 2014; 11: 197-204

Prevention of Recurrent Ischemic Priapism with Ketoconazole: Evolution of a Treatment Protocol and Patient Outcomes

Michael P. Hoeh, MD and Laurence A. Levine, MD
Department of Urology, Rush University Medical Center, Chicago, IL, USA

RIP Ketoconazole Summary:

- Reasonable efficacy / safety
- Cost advantageous
- Sexual function preserved
- Current tapered dose for 6 mo
- ? Long-term effects
- 20-25% need to stay on the medication

Hoeh M and Levine L: J Sex Med, 2014; 11: 197-204

Priapism Economics

Emergency department average cost for one priapism visit:

- If discharged home: \$ 1778.00
- If admitted for hospital stay: \$ 41,909.00

Flum AS. J Sex Med. 2012; 9: 183-298 abs.

Iatrogenic Priapism

- Intracavernosal injections
 - Clinics, ED evaluation, PD evaluation
 - Many with prolonged, painful erections that require further pharmacologic injections, penile aspiration, and/or surgical intervention
 - Persistence of erection can be alarming and exceedingly uncomfortable for patients
 - Reversal more challenging hours after injection

Iatrogenic Priapism

- “Fear” of phenylephrine
- Unfamiliarity; AE concerns
- The majority of Peyronie’s patients undergoing PDDU have no or mild ED
- Ideal study group to evaluate the effects of low-dose phenylephrine as prophylaxis for iatrogenic priapism

Iatrogenic Priapism

- Retrospective review of a group of Peyronie’s disease patients in our practice
- Analyze the safety and efficacy of low dose phenylephrine as prophylaxis against iatrogenic priapism

KJU

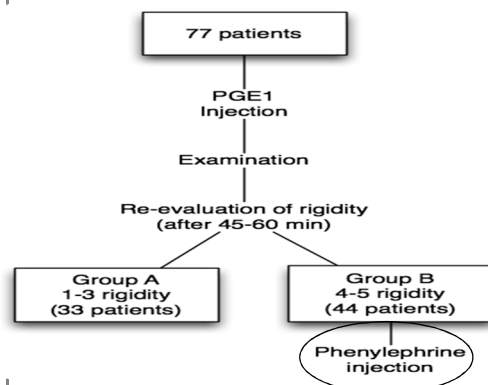
Original Article - Sexual Dysfunction/Male Infertility

Prophylactic Phenylephrine for Iatrogenic Priapism: A Pilot Study With Peyronie’s Patients

Pengbo Jiang¹, Athena Christakos¹, Mina Fam¹, Hossein Sadeghi-Nejad^{1,2}

¹Department of Urology, Rutgers-New Jersey Medical School, Newark, NJ, ²Center for Male Reproductive Medicine & Microsurgery, Hackensack University Medical Center, Hackensack, NJ, USA

- Pilot study of “prophylactic” reversal



Results

- No cases of ER visit post procedure or need for aspiration
- Patients who potentially benefit from “prophylactic” phenylephrine injection can be identified based on post-procedural rigidity

Results

- Group B (4-5 rigidity 15 min post-procedure) → phenylephrine (200 mcg)
- All 44 patients receiving low dose phenylephrine injection achieved complete detumescence.
- No hypotension (mean blood pressure change < 10mmHg),
- No reports of palpitations, or other AEs

KJU

Original Article - Sexual Dysfunction/Male Infertility

www.kjurology.org
http://dx.doi.org/10.4111/kju.2014.55.10.665



Prophylactic Phenylephrine for Iatrogenic Priapism: A Pilot Study With Peyronie's Patients

Pengbo Jiang¹, Athena Christakos¹, Mina Fam¹, Hossein Sadeghi-Nejad^{1,2}

¹Department of Urology, Rutgers-New Jersey Medical School, Newark, NJ, ²Center for Male Reproductive Medicine & Microsurgery, Hackensack University Medical Center, Hackensack, NJ, USA

- Consider “prophylactic” reversal if erection unsubsidized ~ 15 min after completion of duplex Doppler ultrasound study

Conclusion

- Early recognition is key
- Differentiation of Ischemic and Non-ischemic priapism by clinical and laboratory exam is essential
- Ischemic priapism is an emergency
- Non-ischemic : Initial surveillance

Conclusion- Recurrent Ischemic Priapism

1. RIP uncommon - higher prevalence in special populations
2. PDE5 dysregulation
3. Primary management goal is prevention of future episodes
4. Initial Rx similar to ischemic priapism
5. PDE5-Is and KTZ as targeted Rx

THANK YOU!



Female Sexual Health

LEAH MILLHEISER, MD, FACOG

CLINICAL ASSISTANT PROFESSOR, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
DIRECTOR, FEMALE SEXUAL MEDICINE PROGRAM
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Disclosures

- ▶ Advisory Board Member: Valeant Women's Health,
- ▶ Consultant: Amag Pharmaceuticals, Duchesnay USA, Willow Inc., ExploraMed LLC, Aytu BioScience, TherapeuticsMD
- ▶ Employee: Sprout Pharmaceuticals, Inc. (Chief Medical Officer)

Question 1

- ▶ What medication revolutionized the field of female sexual medicine when it was introduced to the market in 1998?

The Little Blue Pill...

Sildenafil

Impetus for developing simple and effective treatments for women

The Impact of Sexual Concerns On a Woman's Quality of Life

- ▶ Studies have demonstrated an association between sexual health and overall health and well-being in both men and women
- ▶ Women who are dissatisfied with their marriage have decreased sense of sensuality
- ▶ Women who have a more satisfying, sexually active life will have a higher degree of satisfaction within their relationship
- ▶ Majority of women in one study reported that decreased sex drive negatively impacted body image & self confidence

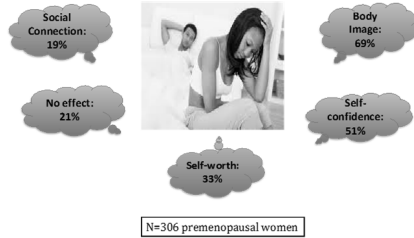
Rust et al. Marital problems and sexual dysfunction: how are they related? B J Psychiat 1988;152:629-31
Marwick C, JAMA. 1999;281(21):73-2174.
Biddle AK, West S, D'Aquila AA, Wheeler SB, Borisov NN, Thorp J. Int Soc Pharmacoecon Outcomes Res (ISPOR). 2009;12:763-772
Kingsberg SA. Attitudinal Survey of Women Living with Low Sexual Desire. J Wom Health 2014; 23(10):817-23

Changes in Sex Drive Have A Negative Impact On A Woman's Relationship

Premenopausal		Postmenopausal
67%	Less connectedness	58%
35%	Less communication	34%
35%	Worry partner will cheat	20%
33%	Argue about it	19%
25%	Worry partner might leave her	17%
9%	No effect	25%

Kingsberg, SA. Attitudinal Survey of Women Living with Low Sexual Desire. J Wom Health 2014; 23(10):817-23.

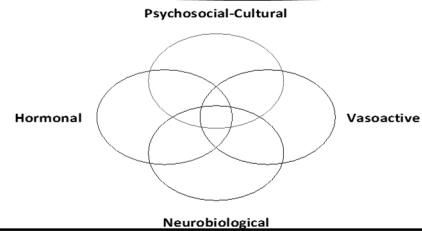
Impact of Low Sexual Desire on Personal Life



N=306 premenopausal women

Kingsberg, SA. Attitudinal Survey of Women Living with Low Sexual Desire. J Wom Health 2014; 23(10):817-23.

The Multifactorial Nature of Female Sexual Function



PHYSIOLOGICAL

Hormonal changes
 Medications
 Chronic illness
 Neurological issues
 Urogenital issues
 Endocrine issues, Fatigue

BIOLOGICAL

Depression
 Stress
 Substance Abuse
 Alcohol
 Domestic, Sexual, Physical Abuse

Multifactorial Nature of Female Sexual Function

INTERPERSONAL

Sexual dysfunction of partner
 Relationship quality and conflict
 Lack of privacy
 Lack of partner

SOCIOCULTURAL

Early education or lack thereof
 Conflict with religious, cultural, personal, and family values
 Societal taboos

Medications With A Negative Impact On Sexual Function

- ▶ Antidepressants & mood stabilizers
- ▶ SSRIs, SNRIs, TCAs, MAOIs
- ▶ Antipsychotics
- ▶ Benzodiazepines
- ▶ Antiepileptics
- ▶ Antihypertensives: beta-blockers, alpha-blockers, diuretics
- ▶ Cardiovascular agents: lipid-lowering agents, digoxin
- ▶ Histamine H2-blockers
- ▶ Hormones: oral contraceptives, estrogens, progestins, antiandrogens, GnRH agonists
- ▶ Narcotics
- ▶ Amphetamines
- ▶ Anticonvulsants
- ▶ Steroids
- ▶ Tamoxifen, aromatase inhibitors

Masters and Johnson – Human Sexual Response Cycle:



Kaplan's Sexual Response Model:

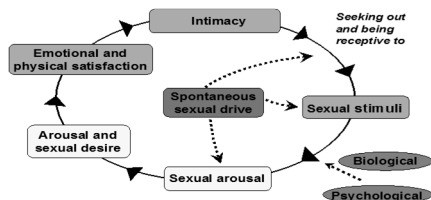


30 Years Later, This Is What Research Has Taught Us About Female Sexual Response

- ▶ Sexual neutrality
- ▶ Fantasy may not reflect desire
- ▶ Desire may be responsive
- ▶ Genital and subjective arousal may not match
- ▶ Satisfaction may not be linked to orgasm
- ▶ Normative lessening (relationship duration/life cycle)

Basson R, et al. J Psychosom Obstet Gynecol. 2003;24:221-9
 Basson R, et al. J Sex Med 2010;7:314-326

Incentive-Based Model of Female Sexual Response



Endorsement of Models of Female Sexual Response

- Aim: to assess extent to which women endorse various models of female sexual function (Masters and Johnson, Kaplan, Basson)
- N=133 pre- and postmenopausal women b/w the ages of 25-69
- Results: approx. equal proportions endorsed all 3 models. Women endorsing Basson model had lower FSFI scores
- Heterogeneity of female sexual response

Sand M, Fisher WA. Women's endorsement of models of female sexual response: the nurses' sexuality study. *J Sex Med* 2007;4(5):708-19

Prevalence of Female Sexual Concerns vs. Dysfunction

Sexual Complaint	Sexual Problem	Sexual Problem + Distress
Desire	38.7%	10%
Arousal	26.1%	5.4%
Orgasm	20.5%	4.7%
Any Dysfunction	44.2%	12%

• N=31,581 women between 18-102 years of age; Mean age: 49

Shifren J et al. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol* 2008;112(5):970-8.

The Classification of FSD

DSM-IV-TR	DSM-V
Hypoactive Sexual Desire Disorder • Sexual Aversion Disorder	Female Sexual Interest/Arousal Disorder
Female Sexual Arousal Disorder	
Female Orgasmic Disorder	Female Orgasmic Disorder
Female Sexual Pain Disorders • Vaginismus and Dyspareunia	Genitopelvic pain/penetration Disorder

ISSWSH: Opposition to FSIAD Classification

- Exclusion of women w/ distressing sexual arousal from diagnosis or treatment
- Women with FSAD may not meet the proposed criteria for FSIAD
- Desire and arousal dysfunctions are mediated by different biological factors
- DSM-IV TR: Premenopausal women with HSDD and women with FSAD have distinct symptom patterns
- Lack of clinical studies to validate the FSIAD diagnosis in the general population or in women w/SD symptoms

Balon R, Clayton AH. Female Sexual Interest/Arousal Disorder: A diagnosis out of thin air. *Arch Sex Behav* 2014;43(7):1227-29.
Clayton AH, Kim DH. Hypoactive Sexual Desire Disorder: Separating fact from fiction. *CNS Spectr* 2016;21(1):9-11.

ISSWSH Female Sexual Disorders Nomenclature (2016)

- **Hypoactive Sexual Desire Disorder:**
 - Lack of motivation for sexual activity
 - Decreased or absent spontaneous desire, decreased /absent responsive desire to erotic cues & stimulation, loss of desire to initiate or participate in sexual activity
- **Female Genital Arousal Disorder:**
 - Inability to develop or maintain adequate genital response (vulvovaginal lubrication, engorgement of genitalia, sensitivity of genitalia associated with sexual activity)
 - Disorders related to: vascular injury or dysfunction and/or neurologic injury or dysfunction
- **Persistent Genital Arousal Disorder:**
 - Persistent or recurrent, unwanted or intrusive, distressing feelings of genital arousal, or being on verge of orgasm
- **Female Orgasm Disorders:**
 - Persistent or recurrent distressing compromise of orgasm frequency, intensity, timing, and/or pleasure a/w sexual activity
- **Female Orgasmic Illness Syndrome:**
 - Peripheral and/or central aversive symptoms that occur before, during, or after orgasm not related to a compromise of orgasm quality

PGAD Risk Factors

- ▶ Spinal conditions: Tarlov cysts, mass/tumor, herniated disc
- ▶ Brain pathology: Trazodone use, abrupt d/c of antidepressant, CVA, seizure disorder
- ▶ Peripheral or central trigger from increased genital engorgement
- ▶ Psychologic conditions: stress, panic disorder, anxiety disorder
- ▶ Genital pathology: vestibulodynia, VVA, clitorodynia, vulvar dermatoses, AV malformations, pudendal neuralgia, high pelvic floor tone, pelvic congestion syndrome, abnormal response to candidal infxn

The Impact Of PGAD

- ▶ Persistent or recurrent, unwanted or intrusive, distressing feelings of genital arousal, or being on verge of orgasm
- ▶ Symptoms a/w despair, frustration, emotional lability, catastrophizing, suicidal thoughts
- ▶ Co-occurrence of OAB and restless leg syndrome
- ▶ Change in orgasm can occur: spontaneous, recurrent, aversive, absent, delayed, muted, or not a/w pleasure, satisfaction
- ▶ Limited to no resolution of symptoms, or worsening of symptoms, with orgasm

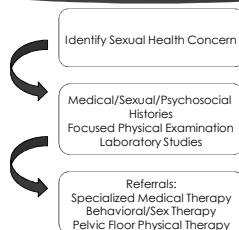
PGAD Work Up

- ▶ History:
 - ▶ Neurological or vascular disorders
 - ▶ Spinal/back trauma/pelvic trauma
 - ▶ Psychiatric disorders: e.g., anxiety, depression, OCD
 - ▶ Medications
- ▶ Exam:
 - ▶ Genital exam: trigger point testing, assess for varices
- ▶ Labs:
 - ▶ Low utility for making diagnosis but can check hormone levels
- ▶ Imaging:
 - ▶ Pelvic uls w/doppler (varices)
 - ▶ Spinal MRI, pelvic MRI, EEG

Treatment of PGAD

- ▶ No FDA-approved approved therapy for PGAD
- ▶ No consensus on treatment
- ▶ Try to identify and address specific inciting factor:
- ▶ If no inciting factor identified:
 - ▶ Conservative measures: meditation/relaxation, avoidance of factors that worsen symptoms (sexual thoughts, pressure applied to the vulvar)
 - ▶ Behavioral Therapy
 - ▶ Physical Therapy: pelvic floor relaxation, TENS
 - ▶ Sacral neuromodulation, Pudendal nerve blocks
 - ▶ Pharmacologic: neuromodulators, topical lidocaine, SSRI/SNRI, vilazodone, tramadol, varenicline

Diagnosing Female Sexual Dysfunction In 3 Easy Steps



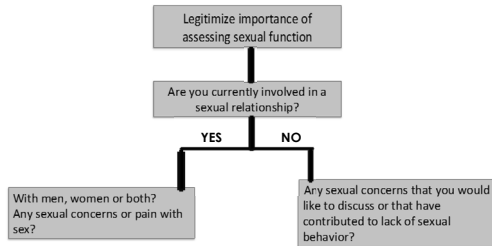
ALLOW Algorithm

Managing sexual dysfunction in the office setting:

- ▶ "A": Ask
- ▶ "L": Legitimize
- ▶ "L": Limitations → Refer
- ▶ "O": Open up for further discussion and evaluation
- ▶ "W": Work together to develop a treatment plan

Sadovsky R, Mulhall JP. Int J Clin Pract. 2003;57:601-608

Basic Screening for Sexual Function



The Biopsychosocial History

Histories: Medical, psychosexual

Brief Validated Questionnaires:

Female Sexual Function Index (FSFI)

Helps id area of sexual concern

Identifies who's at risk for FSD

Does not diagnose FSD

Female Sexual Distress Scale-R (FSDS-R)

Helps in making diagnosis of FSD by assessing distress a/w sexual concern

Helps assess response to treatment

Decreased Sexual Desire Screener (DSDS):

Helps identify patients who may have acquired, generalized HSDD

DSDS: Diagnostic Tool for HSDD

"No" to Q 1,2,4, or 4 → not generalized, acquired HSDD

"Yes" to Q 1,2,3,4 and "No" to Q 5 → generalized, acquired HSDD

"Yes" to Q 1,2,3,4 and "Yes" to any Q5 → clinician uses best judgment to decide if HSDD

Name: _____ Age: _____ Date: ____/____/____

- In the past, was your level of sexual desire or interest good and satisfying to you? Yes No
- Has there been a decrease in your level of sexual desire or interest? Yes No
- Are you bothered by your decreased level of sexual desire or interest? Yes No
- Would you like your level of sexual desire or interest to increase? Yes No
- Please circle all the factors that you feel may be contributing to your current decrease in sexual desire or interest:

A. An operation, depression, injuries, or other medical condition	Yes	No
B. Medications, drugs, or alcohol you are currently taking	Yes	No
C. Pregnancy, recent childbirth, menopausal symptoms	Yes	No
D. Other sexual issues you may be having (pain, decreased arousal or orgasm)	Yes	No
E. Your partner's sexual problems	Yes	No
F. Dissatisfaction with your relationship or partner	Yes	No
G. Stress or fatigue	Yes	No

Flibanserin: Acquired, Generalized HSDD

- Flibanserin is the only drug FDA-approved for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:
 - A co-existing medical or psychiatric condition,
 - Problems within the relationship, or
 - The effects of a medication or other drug substance
- FDA approval in 10/15
- Classified as a multifunctional serotonin agonist antagonist
 - 5HT_{1A} agonist, 5HT_{2A} antagonist
 - Animal studies: flibanserin increases dopamine and norepinephrine levels and decreases serotonin levels in the prefrontal cortex and hypothalamus.

Flibanserin: Boxed Warning

WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

See full prescribing information for complete boxed warning

- Use of flibanserin and alcohol increases the risk of severe hypotension and syncope; therefore alcohol use is contraindicated. Before prescribing flibanserin, assess the likelihood of the patient abstaining from alcohol. Counsel patients prescribed flibanserin about the importance of abstaining from alcohol.
- Flibanserin is available through a restricted program called the flibanserin REMS program.
- Severe hypotension and syncope can occur when flibanserin is used with moderate or strong CYP3A4 inhibitors or in patients with hepatic impairment; therefore, flibanserin use in these settings is contraindicated.

Bremelanotide: HSDD

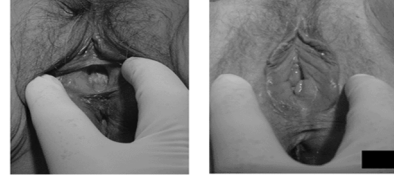
- Investigational melanocortin 4 receptor agonist
- On-demand treatment for premenopausal women w/ HSDD
 - Single-use subcutaneous injection (autoinjector pen)
 - June, 2018: FDA accepted Bremelanotide NDA
- Ph. 3 RECONNECT studies: DeRogatis L, et al. JSM 2017;14(6), Supplement S6356
 - 2 double-blind, placebo-controlled, randomized parallel group studies: bremelanotide 1.75mg vs. placebo
 - Over 600 premenopausal women in each group (n: 1,202)
 - Study Duration: 24 weeks, mean age 39
 - Co-primary Endpoints were met: statistically significant improvement in desire and decrease in distress for bremelanotide compared to placebo
 - Validated PROs: FSFI-Q, FSDS-DAD Item 13
- Most common AEs: nausea, flushing, headache

Genitourinary Syndrome of Menopause

- ▶ GSM is chronic and progressive
- ▶ Affects up to 50% of midlife and older women (Management of symptomatic vulvovaginal atrophy:2013 position statement of NAMS. Menopause 2013;20:888-902)
- ▶ Symptoms:
 - ▶ Genital dryness, burning, irritation, decreased genital arousal/orgasmic intensity
 - ▶ Poor vaginal lubrication during sex, discomfort with sex, impaired sexual function, postcoital bleeding
 - ▶ Urinary urgency, dysuria, recurrent UTIs

Vaginal Atrophy

Effects of Reinitiating Topical Estrogen Therapy



*Patient image represents the atrophic appearance several years after menopause and reveals the inflammatory changes and atrophy.

*Patient image represents the "normalization" of the appearance after 3 months of topical estrogen therapy.

Copyright Murray A. Freedman, MS, MD, 2008

Medscape

Tx of GSM: Vaginal Estrogen

- ▶ More effective than systemic estrogen for treating GSM
- ▶ Very low doses can be used to achieve beneficial effects on vaginal epithelium
- ▶ Low systemic absorption → minimizes impact on endometrium, breast
 - ▶ Avoid breast tenderness, endometrial stimulation, and withdrawal bleeding
- ▶ Does not relieve vasomotor symptoms or preserve bone mineral density

Nonestrogen Therapies: Postmenopausal VVA + Dyspareunia

Ospemifene (Selective Estrogen Receptor Modulator)

- ▶ SERM, Route: oral; Hot flashes; most frequent TEAE (6.6% vs. placebo 3.6%)
- ▶ No need for endometrial protection
- ▶ Ph 3 MCT: Ospemifene showed statistically significant improvement over placebo in lowering vaginal pH, decreasing parabasal cells, & reducing dyspareunia

Prasterone (Intravaginal DHEA):

- ▶ Approved by FDA in 11/16
- ▶ Only FDA-approved, local non-estrogen product for dyspareunia due to menopausal VVA
- ▶ Intracellular conversion of DHEA to estrogen (estradiol) and androgen
- ▶ Daily use; Minimal systemic exposure
- ▶ Has not been studied in women with breast cancer

Prasterone Research

- ▶ Phase III clinical trial: to confirm local effects of prasterone on moderate to severe dyspareunia (Archer DF et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). Menopause 2015;22(9):950-6)
- Daily intravaginal prasterone for 12 weeks (6.5mg)
- Clinically and statistically significant beneficial effects on 4 co-primary objectives of VVA (% of vaginal parabasal cells, % of vaginal superficial cells, vaginal pH, moderate to severe dyspareunia)
- Serum steroid levels remained w/in normal postmeno range
- Most common AE: vaginal discharge from melting suppository (6%)
- No change in endometrial atrophy after 12 months (D. Portman, et al. Menopause 2015)

Low Dose Vaginal Estrogen Therapy in Women With A History Of Estrogen-Receptor Positive Breast Cancer

- ▶ Low-dose vaginal estrogen should be used only as 2nd line therapy if nonhormonal tx not effective
- ▶ Potential risk of small increase in circulating estrogens
- ▶ However, no increased risk of breast cancer recurrence in AI and tamoxifen users with low-dose vaginal ET during mean 3.5 yr follow up
- ▶ Decision about low-dose vaginal ET should involve oncologist

LeRoy J et al. Loc of estrogen therapy and risk of breast cancer recurrence among hormone-treated patients: a nested case-control study. Breast Cancer Res Treat 2012;135
ACOG Committee Opinion, 03/16

Use of Vaginal Estrogen In Women With A History Of Estrogen-Dependent Breast Cancer

► **ACOG Committee Opinion, 3/16:**

- To treat the hypoestrogenic-related adverse effects of cancer therapies or of natural menopause in survivors
- Vaginal estrogen should be reserved for patients who are unresponsive to non-hormonal remedies
- Decision should be made in coordination w/a woman's oncologist
- Data does not show increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen

OTC Options For Addressing Dyspareunia Related to GSM

1. Vaginal Moisturizers
2. Personal Lubricants
3. Skin Barriers



Nonhormonal Vaginal Moisturizers

- Non-prescription, long-term relief of vaginal dryness
- Replenish water content to vagina, improves elasticity
- Longer duration of effect than personal lubricants
- Often used for the treatment of atrophic vaginitis (vaginal dryness, itching)
- Widely-available

Personal Lubricants

- Relief of vaginal dryness/dyspareunia during sexual activity
- Diminishes discomfort due to friction
- Applied around external genitalia & inside vagina
- Short duration of action
- Types:
 - Water-based
 - Silicone-based
 - Oil-based

Water-Based Lubricants

- Most widely available
- Safe to use with latex condoms, sex toys
- Tend to dry up quickly
- Reactivate with water
- Do not stain
- Rarely cause irritation
- Common ingredients: deionized water, glycerin, propylene glycol
- Available in glycerin-free options
- Glycerin may promote vaginal inflammation and yeast infection

Oil-Based Lubricants

- **Petroleum-based:**
 - Petroleum jelly, mineral oil, baby oil
 - May promote vaginal inflammation/irritation
 - Not for use with latex condoms
 - Can reduce both the effectiveness of latex items and prevention of STDs
- **Natural oils:**
 - Coconut, avocado, corn olive, peanut,
 - Non-irritating
 - Should not be used with latex items

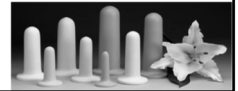


Silicone-Based Lubricants

- ▶ Longer lasting than water-based lubricants
- ▶ Can be used in water
- ▶ Safe to use with latex condoms, diaphragms, non-silicone toys
- ▶ Available in glycerin-free options
- ▶ Can be used as a massage oil
- ▶ More expensive than water-based lubricants
- ▶ Harder to wash off sheets and clothing

Vaginal Stenosis - Treatment

- ▶ Mainstay of therapy:
 - ▶ Vaginal dilator
 - ▶ May consider topical anesthetic, if necessary
 - ▶ Vaginal estrogen
 - ▶ Non-hormonal therapy is estrogen contraindicated
- ▶ Duration of therapy is variable
- ▶ "If you don't use it, you lose it"
- ▶ Pelvic Floor PT



Vaginal Rejuvenation

- ▶ Marketing, not medical, nomenclature
- ▶ Umbrella term to describe aesthetic and functional procedures to correct/restore the vagina and surrounding tissues
- ▶ Treatment Spectrum:
 - ▶ Noninvasive → lubricants, hormone therapy, kegel exercises, **energy-based systems**
 - ▶ Invasive → vaginoplasty, labiaplasty, etc.

Benefits of Energy Based Systems

- ▶ Non-invasive
- ▶ Avoids surgical risk
- ▶ Less expensive than surgery
- ▶ Less downtime than surgery
- ▶ Can be performed by wider range of practitioners (e.g., NP, PA)

Fractional CO2 Laser: Treatment of GSM

- ▶ Fractional microablative CO2 laser: originally designed for tx of acne scars, skin resurfacing and rejuvenation
- ▶ Laser generates heat and vaporizes the water content of target cells
- ▶ Production of new collagen and elastic fibers, remodeling of connective tissues
- ▶ Improves vaginal elasticity and hydration of the vaginal walls/ relieves discomfort during penetrative intercourse

Perino A, et al. Vulvo-vaginal atrophy: a new treatment modality using thermo-ablative fractional CO2 laser. *Maturitas* 2011;80(3):294-301

Fractional CO2 Lasers

- ▶ 510k cleared for the following indications:
 - ▶ incision, excision, ablation, vaporization & coagulation of body soft tissues in medical specialties
- ▶ It is not cleared for the treatment of vulvovaginal atrophy (VVA)

Fractional CO2 Laser Research

- ▶ Athanasiau S. et al.: improvement in prevalence of normal vaginal flora (lactobacillus) in postmenopausal women & reduction in vaginal pH after 3 treatments
- ▶ Sokol E. and Karam M.: Statistically significant improvement in vaginal pain, burning, itching, dryness, dyspareunia, and dysuria; no adverse events
- ▶ Sokol E. and Karam M.: statistically significant improvement in VVA symptoms through 1 year following treatment
- ▶ Pieralli A. et al.: significant improvement in VVA symptoms in breast cancer survivors after 3 treatments; 52% were satisfied after 11 months. No adverse events

No sham arm studies, 1 laser retreatment usually indicated after 1 year

FDA Warns Against Use Of Energy Based Devices For Vaginal Rejuvenation Procedures

July 30, 2018:

- ▶ Safety and effectiveness of energy-based devices to perform vaginal "rejuvenation" or cosmetic vaginal procedures has not been established
- ▶ FDA has not cleared or approved any energy-based medical device for vaginal "rejuvenation" or vaginal cosmetic procedures, or for the treatment of vaginal symptoms related to menopause, urinary incontinence, or sexual function
- ▶ Discuss the benefits and risks of all available treatment options for vaginal symptoms with your patients

Common FSD Referrals

- ▶ Find a FSD specialist in your area:
www.iswsh.org
- ▶ Find a pelvic floor physical therapist in your area: www.apta.org
- ▶ Find a certified sex therapist in your area:
www.aasect.org
www.sstarnet.org

THANK YOU

Genital surgery for the MtF Transgender patient

Robert Oates, MD

Boston Medical Center
Boston University School of Medicine

Disclosures

- No industry relationships to disclose
- No financial relationships to disclose

Transgender Care at Boston Medical Center

- Center for Transgender Medicine and Surgery (CTMS)
 - Coordination of care
 - Multidisciplinary approach
 - Endocrinology, Urology, Plastic Surgery, Internal Medicine, Nursing
 - Psychiatry, Behavioral Therapy, Social Work, Physical Therapy
 - Gynecology, Podiatry, ENT, Dermatology, Surgical Oncology
 - Indication/Approval Committee
 - Endocrinologist, Urologist, Plastic Surgeon, Nurse Practitioner
 - Social Worker, Psychiatrist, Team Leader (Internist), Coordinator
 - Financial
 - Surgeons and clinic / hospital

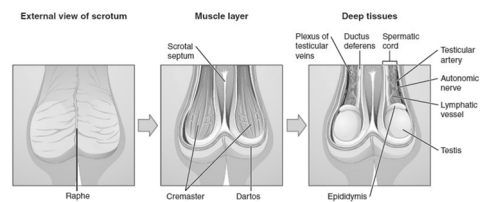
Types of 'Bottom Surgery'

- Orchiectomy
- Neovaginoplasty
- "Genital Remodeling" (zero-depth vaginoplasty)

Goals of Surgery : Orchiectomy

- Alignment of anatomy with body image
 - Slightly less scrotal bulk
- Relief of psychological discomfort
 - The knowledge there are no testicles
- Elimination of spironolactone
 - Used in conjunction with estrogens
 - Blocks testosterone action/production
 - Has intrinsic estrogenic effect
- Improved estrogenic effect
 - If Leydig cells not totally suppressed
- May be prior to full surgery
 - Neovaginoplasty / Genital Remodeling
 - Do not remove scrotal skin
- Will not compromise future surgery
 - Neovaginoplasty / Genital Remodeling
- Need to ask about parenthood !

Surgical Technique: Orchiectomy



Anatomy & Physiology, Connexions Web site. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013

Untoward events after orchiectomy

- Scrotal hematoma
 - rare
- Incision breakdown
 - rare
- Discomfort at end of spermatic cord
 - unusual
- Decreased libido and erection
 - Depends on level of pre-op T
 - If high, may experience hypogonadism
 - If castrate, essentially no change
- Decreased ejaculate volume
 - Depends on level of pre-op T
 - If high, may experience reduction
 - If castrate, essentially no change

Goals of Surgery : Neovaginoplasty

- Alignment of anatomy with body image
- Relief of psychological discomfort
- One of the final stages of gender-confirming process
 - Augmentation mammoplasty
 - Facial feminization
- Feminine appearing vulva
- Hooded and sensate clitoris
- Urethral meatus properly located
- Vaginal depth sufficient for penetration (Neovaginoplasty)
 - If necessary

Goals of Surgery : vaginal depth

- Heterosexual orientation
 - Penetrative intercourse
 - Amount of tissue available
 - Penile
 - Scrotal
 - Lower abdomen
 - Peritoneum
 - Colon
- Lesbian Orientation
 - Penetrative sexual activity
 - Toys / dildos
 - "How deep?"
 - Non-penetrative sexual activity
 - Still desirous of vagina
 - "How deep?"

Important to individualize !!

Desired Outcomes : Neovaginoplasty

- Improved mental health scores after surgery (GRS or FFS)
- Good satisfaction with appearance and self image
- Lowers dysphoria
- Improved well-being
- Clitoris with dorsal hooding- sensate
- Mucosal strip: well perfused
- Proper urethral function / location
- Labial symmetry
- Functional vagina

Patient Selection: CTMS at BMC

- Established dx of gender identity disorder (F64.0)
- Two letters of recommendation
 - Behavioral Health
- 18 years or older
- Hormonal therapy of >1 year
- Real-life experience for >1 year
- BMI < 32
- Non-smokers
- Non-diabetics
 - At least well-controlled
- Good general health
- Genital hair removal

Patient Selection: CTMS at BMC

- Follow WPATH Guidelines
 - World Professional Association for Transgender Health
- Slight local modifications
 - Smoking, BMI considerations, when to stop estrogens, etc

Preoperative requirements : Neovaginoplasty

- Genital hair removal
 - Penile and scrotal skin
 - Midline distribution
 - Base of scrotum down to anus (2" strip)
 - NOT lateral to penis or scrotum
- Laser hair removal
- Electrolysis
- Some insurers may cover cost



https://commons.wikimedia.org/wiki/File:Flaccid_penis_cropped.jpg

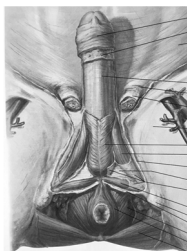
Preoperative requirements : Neovaginoplasty

- Discontinue estrogen 4 weeks prior
 - To prevent DVTs
 - No hard data to support
- Bowel prep day before
 - In event of rectal injury



https://commons.wikimedia.org/wiki/File:Flaccid_penis_cropped.jpg

Relevant anatomy : Neovaginoplasty

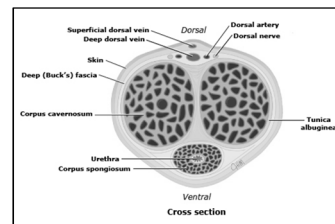


Skin
Superficial fascia (dartos)

Deep fascia (Buck), urethra/corpus spongiosum
Spermatic cord
Bulbospongiosus muscle
Ischiocavernosus muscle

Superficial transverse perineal muscle

Cross section of the penis



Vascular and neural anatomy

VASCULAR

- Deep
 - Internal pudendal a.
 - Perineal a.
 - Scrotal a.
 - Common penile a.
 - Dorsal a. of penis
- Superficial
 - External pudendal a.
 - Superficial
 - Deep

NERVE

- Deep
 - Pudendal nerve (S2-S4)
 - Perineal n.
 - Dorsal n. of penis
- Superficial
 - Ilioinguinal n.
 - Genitofemoral n.

Surgical Technique : Neovaginoplasty



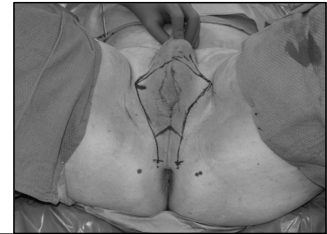
Surgical Technique : Neovaginoplasty

- Epidural catheter
- Lithotomy position
- Perioperative antibiotics
 - cefazolin
 - metronidazole



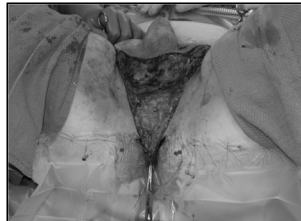
Surgical Technique : Neovaginoplasty

- Markings
 - Perineal flap
 - Scrotal skin



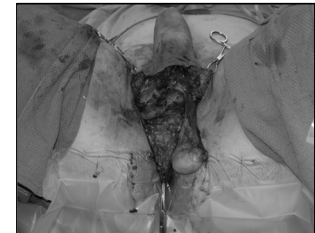
Surgical Technique : Neovaginoplasty

- Elevation of perineal flap
- Deepithelialization of scrotal skin
 - May be used as a free graft
 - Attached to "top" penile skin



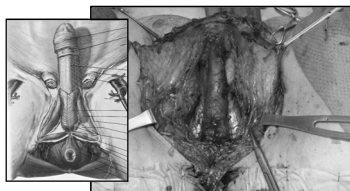
Surgical Technique : Neovaginoplasty

- Orchiectomy
 - Take cord at external ring
 - Specimens to pathology



Surgical Technique : Neovaginoplasty

- Penile dissection
 - Move tissues laterally
 - Expose corpus spongiosum
 - Overlying bulbospongiosus muscle
 - Down into perineum
 - Expose both corpus cavernosa
 - Overlying ischiocavernosus muscle



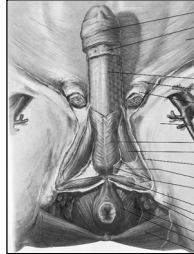
Surgical Technique : Neovaginoplasty

- Bulbospongiosus muscle
 - Originates laterally
 - Attaches in midline raphe
 - Simply surrounds corpus spongiosum
 - Anteriorly
 - Finger can be inserted in that space to elevate and allow cautery dissection off
 - Complete removal into perineum



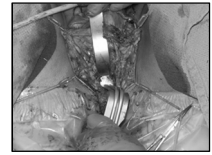
Surgical Technique : Neovaginoplasty

- Dissection of neo-vaginal canal
- Take down midline perineal body below sponge
- Dissect lateral to this as well
- Push corpus spongiosum anteriorly
- Push rectum posteriorly
- Gently, Gently, Gently create more space
 - Superiorly to above trigone



Surgical Technique : Neovaginoplasty

- Cauterize bleeding points
 - Recto-urethralis muscles
 - External rectal serosal vessels
- May irrigate rectum
 - Betadine solution
 - If not sure of rectal wall integrity
- Pack with lap pad and move to penile dissection



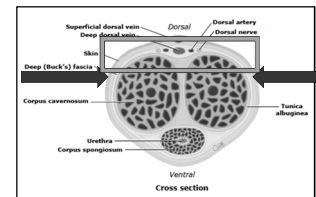
Surgical Technique : Neovaginoplasty

- Degloving of penis
- Leave dorsal hood
 - circumcision incision
- Creates penile skin tube
 - Forms neovagina



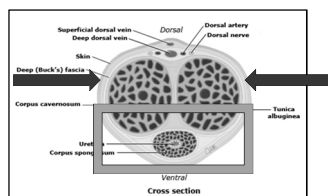
Surgical Technique : Neovaginoplasty

- Deconstruction of penis
 - Separation of urethra
- Lateral opening on each corpora
 - Removal of cavernosal tissue
- Create strip of dorsal tunica albuginea
 - NV bundle intact
 - Some prefer to dissect NV bundle to root
 - Glans intact on top
 - Will become neoclitoris

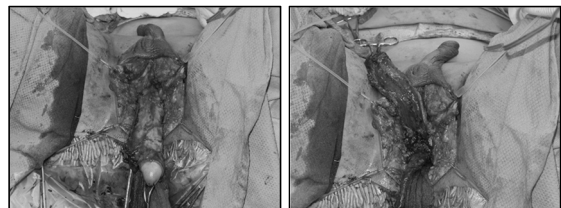


Surgical Technique : Neovaginoplasty

- Ventrally
- Corpus spongiosum
- Urethra and catheter

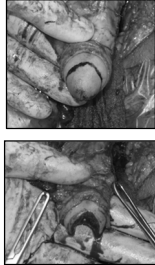


Surgical Technique : Neovaginoplasty



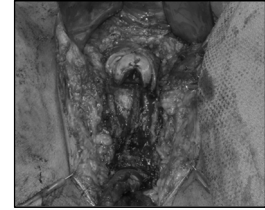
Surgical Technique : Neovaginoplasty

- Formation of neo-clitoris
 - Remove glans tissue
 - Create inverted V



Surgical Technique : Neovaginoplasty

- Inset of neo-clitoris
 - Tack to underlying tissue
 - Between adductor longus tendons



Surgical Technique : Neovaginoplasty

- Inset of urethra
- Anatomically correct position
- Midline and straight



Surgical Technique : Neovaginoplasty

- Mature urethra
- Mature neo-clitoris
- Mucosal strip up to neoclitoris
- Inset of perineal flap
 - Into penile skin tube



Surgical Technique : Neovaginoplasty

- Preparation of skin graft
- Scrotal skin removed at beginning
- Tubularized



Surgical Technique : Neovaginoplasty

- Inset of skin graft
 - Attached to penile skin tube
- Whole construct inverted
 - Neovaginal space
- Tailor-tacking of labia majora



Surgical Technique : Neovaginoplasty

- Packing : Important
- Inserted into neovagina
- Keeps it distended and in place
- Fixes it to surrounding tissues
- Allows free graft to vascularize



Surgical Technique : Neovaginoplasty

- Retention sutures
- Keeps everything in place
- Compression on mucosal strip



Postoperative Care

- Regular diet
- Antibiotics x 24 hrs
- Bed rest x 2 days
- Epidural removed on POD#2
- Discharge home POD#3
- Packing and foley removed on POD#6
- Dilation starts immediately after packing is removed

Untoward postoperative events - literature review -

SHORT TERM

- Infection (4-16%)
- Bleeding (2-10%)
- Necrosis (0.6-24%)
- UTI (4.4%)
- Urinary retention (12.8%)
- Prolapse (4.4%)
- Urethral injury (1.1-3.6%)
- Rectal injury (0.4-4.5%)
- Recto-neovaginal fistula (1-3%)

LONG TERM

- Neovaginal stenosis (1-12%)
- Urethral fistula (1.7%)
- Abnormal urine stream (10-20%)
- Meatal stenosis (1-40%)
- Partial prolapse (1-4%)
- Need for secondary corrections (33.7)
- Need for revision vaginoplasty (2.9%)

Vaginal canal
necrosis



Hematoma requiring transfusion
Urethral strip slough



Vaginal prolapse
Retained bulbospongiosus
Abnormal urine stream



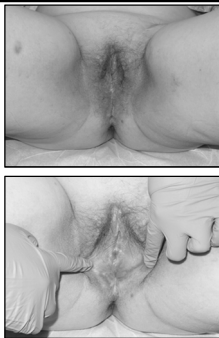
Posterior vaginal introitus web



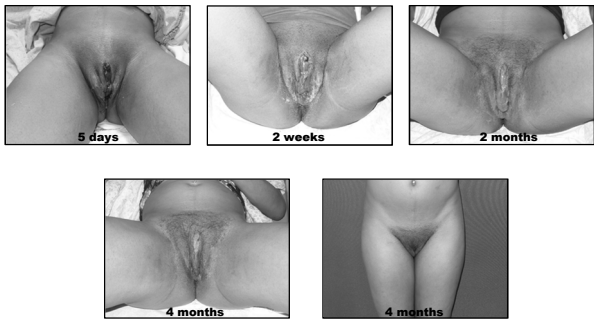
Vaginal stricture

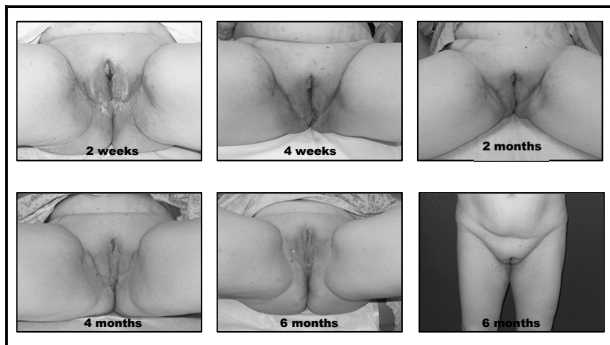


Vaginal atresia



Results





Goals of Surgery : Genital Remodeling

- Alignment of anatomy with body image
- Relief of psychological discomfort
- One of the final stages of gender-confirming process
 - Augmentation mammoplasty
 - Facial feminization
- Feminine appearing vulva / labia
- Hooded and sensate clitoris
- Urethral meatus properly located
- No vagina
 - No need for dilation
 - No need for hair removal
 - No complications from the vagina

Goals of Surgery : Genital Remodeling

- Older individuals
- No desire for penetrative sexual activity
- No "need" for the vagina
- Strong "need" for feminine appearance
- Discharge following day
- Foley and compressive dressing
 - Remove POD#5

Excellent option for some patients: not everyone requires full neovaginoplasty

Conclusion

- Neo-vaginoplasty is an established component of treatment of gender dysphoria
- Penile inversion neo-vaginoplasty is an established gold-standard technique
- Growing demand

Future Directions

- More outcome studies are necessary
- Need for formal education and training of surgeons
- Multidisciplinary approach to care of patients with gender dysphoria

thank you

Cancer of the Testis

Joel Sheinfeld, M.D.
Florence & Theodore Baumritter/
Enid Ancell Chair of Urologic Oncology
Deputy Chief Urology Service
Memorial Sloan Kettering Cancer Center

Disclosure Statement

Nothing to disclose

Testicular Cancer Trends in Survival for all Stages

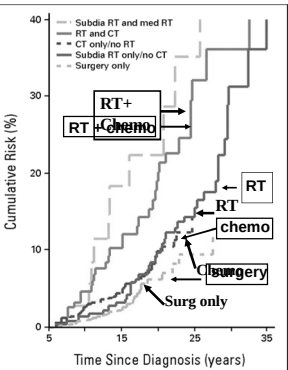
Years	5-yr Survival (%)
1960 - 63	63
1970 - 73	72
1974 - 76	79
1977 - 79	88
1983 - 88	93
1989 - 96	95
2005 - 11	97

Reducing Morbidity and Testing Lower Bounds of Efficacy

Germ Cell Tumors: Special Features (overall 5 year survival ~ 97%)

- Occurrence in young adults
late toxicity (2nd malignancies, CV events)
late relapse (> 2 years after CR)
- Chemosensitive
- Consistent pattern of metastasis
- Produces marker proteins (AFP/ HCG)
- Capacity to differentiate: teratoma

Late Toxicity After GCT Treatment Competing Risks: 2nd Cancers and Heart Disease



1. **Chemo or RT:**
Risk of SMN or CVD greater than after RPLND.
2. **RT + Chemo**
Risk greater than either Chemo or RT.

Testicular Tumors Epidemiology

Approximately 8,500 new cases in US in 2018

Approximately 350 deaths in US in 2018

Most common solid malignancy in men ages 15-34 years

Incidence increasing worldwide; more than doubled in last 40 years

Germ cell tumors: 96%

2-3% incidence bilateral tumors

Frequency of Germ Cell Tumor Histology

<u>Histology</u>	<u>Frequency</u>	<u>Stage I</u>	<u>Stage II</u>	<u>Stage III</u>
Seminoma	50%	70%	20%	10%
Cure Rate	----	99%+	~98%	~90%
NSGCT	50%	33%	33%	33%
Cure Rate	----	99%+	~90%	70%-80%

GCT: Risk Factors

Cryptorchidism

3 -14 times increased incidence

5% - 10% develop tumor in normally descended testicle

Atrophic testicle

Infertility/subfertility:10%-15% GCT diagnosed during fertility w/u

Family history: 8-10 fold increased risk for brothers;
4-6 fold increased risk for fathers and sons

Cannabis ??

Testicular Tumors: Diagnosis

A solid, firm, intratesticular mass is testicular cancer until proven otherwise. Radical orchiectomy is indicated.

Delay in diagnosis very common and can result in more advanced stage, increased burden of therapy and decreased survival (NSGCT).

.

Delay in diagnosis: patient +/- physician(s)



Back pain for 8 months



GI symptoms for 4 months

Testicular Tumors--Presentation

LOCAL

Painful swelling, dull ache

Hard firm painless mass (pathognomonic)

METASTATIC SITES

Back pain (RP metastasis)

Neck mass [supraclavicular node(s)]

Cough (pulmonary metastasis)

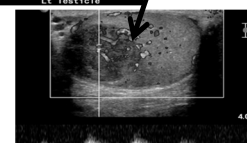
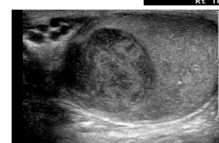
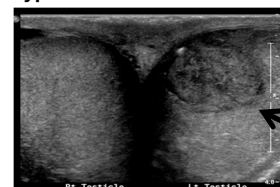
GI symptoms (mass)

CNS symptoms (brain metastasis)

Lower extremity swelling (iliac or IVC thrombus)

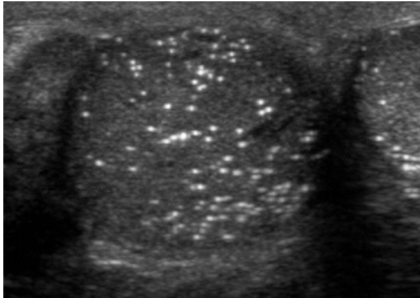
Gynecomastia 5%-10% cases

Scrotal sonography with doppler images hypochoic vascular lesion(s)



Solid intratesticular mass is a tumor until proven otherwise. Rx is radical orchiectomy

microlithiasis



A 5-Year Followup Study of Asymptomatic Men With Testicular Microlithiasis

Brian J. DeCastro, Andrew C. Peterson* and Raymond A. Costabile

From the Department of Urology, Madigan Army Medical Center, Tacoma, Washington, and University of Virginia School of Medicine, Charlottesville, Virginia

Purpose: Testicular microlithiasis is an imaging entity of the testicle with questionable significance as a marker for testicular cancer. **Methods:** We reported on a large prospective screening study establishing the prevalence of testicular microlithiasis (TM) in a healthy asymptomatic population of Army volunteers 18 to 35 years old. In contrast, testicular cancer develops in only 1 of 100,000 men. Two-year followup of 63 of the 84 patients with testicular microlithiasis showed that none of these men had testicular cancer or scrotal masses. Here we report the 5-year followup in this cohort of men with testicular microlithiasis at risk for testicular cancer.

Materials and Methods: According to the original parameters of the screening study we performed a history, genitourinary examination and scrotal ultrasound on 1,504 healthy army volunteers 18 to 35 years old during summer military training. Testicular microlithiasis was defined as greater than 6 echogenic signals found on ultrasound. We identified 84 patients with testicular microlithiasis (5.6%). These men were entered into the followup phase of the study and instructed regarding

Comparison of followup studies			
	No. Pts With TM (%)	No. Pts Contacted/ Total No. Pts (%)	No. Pts With TC (%)
Original study (2000)	84 (5.6)	Not available	0 (0)
2-Yr followup (2002)	84	64/84 (76.2)	0 (0)
5-Yr followup (2005)	80	63/80 (78.8)	1/63 (1.59)

Conclusion: Testicular cancer will **NOT** develop in majority of men with microlithiasis with follow-up of 5 years. Intensive screening not cost effective. Recommend self-examination in men at risk.

Testicular Microlithiasis Predicts Concurrent Testicular Germ Cell Tumors and Intratubular Germ Cell Neoplasia of Unclassified Type in Adults

A Meta-Analysis and Systematic Review

Iain B. Tan, MD¹; Kai K. Ang¹; Boon C. Ching, MD²; Chandra Mohan, MD³; Chee K. Toh, MD³; and Min H. Tan, MD¹

BACKGROUND: There is an increasing body of literature associating testicular microlithiasis (TM), a common finding on testicular ultrasound, with testicular germ cell tumor (TGCT) and intratubular germ cell neoplasia of unclassified type (ITGCNU). Determining these associations is pertinent both clinically and biologically. To the authors' knowledge, no previous systematic review or meta-analysis has been performed. **METHODS:** A comprehensive systematic literature review was performed without language restrictions through July 2009 and included an exhaustive search of electronic databases and article references. Two reviewers extracted data independently. Studies were categorized according to the clinical context in which sonography was performed. The primary study outcomes were concurrent diagnoses of TGCT or ITGCNU, with TM. In addition, studies with prospective follow-up of patients with TM were reviewed. **RESULTS:** Thirty-three studies met inclusion criteria. TM was associated with an increased risk of TGCT in asymptomatic men. However, in referral populations, TM was associated overall with a risk ratio of 8.5 (95% confidence interval [CI], 4.5-16.1; $P < .001$) for a concurrent diagnosis of TGCT and 10.5 (95% CI, 5.3-20.8; $P < .0001$) for ITGCNU. Seventeen observational studies were identified in which the interval development of TGCT in patients with TM was reported; however, the majority of those studies did not report the follow-up of a control arm and could not be summarized. **CONCLUSIONS:** In the presence of risk factors, TM was associated with a substantially elevated risk of a concurrent diagnosis of TGCT and ITGCNU. The authors suggest modifications to recently proposed guidelines for the management of TM. *Cancer* 2010;116:4520-32. © 2010 American Cancer Society.

KEYWORDS: testicular microlithiasis, germ cell neoplasms, testicular carcinoma in situ, meta-analysis.

Sperm banking and testicular surgery

Sperm banking PRE - orchiectomy

Solitary testicle

Bilateral masses

History of contralateral orchiopexy

Atrophic contralateral testicle

Testicular Tumors: Clinical Evaluation

History / Physical Exam

Scrotal US

Serum AFP, HCG, LDH

CT Abdomen, Pelvis

CT Chest vs CXR

MRI brain: pure choriocarcinoma; neurologic sx's

PET scan

- no role in initial staging
- no better accuracy over CT
- post-chemo seminoma (does not distinguish teratoma from fibrosis)

PET SCAN in LOW-STAGE GCT

NO ROLE in staging or follow-up of low stage GCT

Excess radiation; excess \$\$\$

Adherence to National Comprehensive Cancer Network Guidelines for Testicular Cancer

Kevin M. Wymer, MD¹, Shane M. Pearce, MD², Kelly T. Harris, MD³, Phillip M. Pierorazio, MD³, Siamak Daneshmand, MD⁴, Scott E. Eggener, MD⁵ 

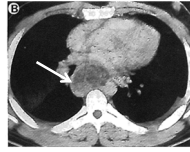
27% of patients with inappropriate PET scan had Stage I GCT (NSGCT >> Seminoma)

5% of CSI patients had inappropriate PET scan

Wymer et al. *J Urol*; 2016

Improved Chest Staging with CT vs CXR

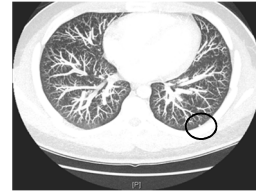
CXR can miss mediastinal disease



CXR misses small pulmonary nodules



27 yo old S/P R orch: NSGCT (+) LVI
CT abd/pelvis normal; STM normal



4 weeks later



Testicular Cancer Serum Tumor Markers

- Diagnosis
- Staging (TNM^S)
- Monitoring response to therapy
- Monitoring for tumor recurrence
- Predicting prognosis and risk-directed therapy
(in both low stage and advanced GCT)

Serum Tumor Markers

HCG

Produced by
syncytiotrophoblasts

Half-life: 18-36 hours

False positive
Cross-reaction LH
Treatment induced hypogonadism
Pituitary production of HCG

Testosterone suppression test

Seminoma ~ 10% elevated
(no prognostic impact)

AFP

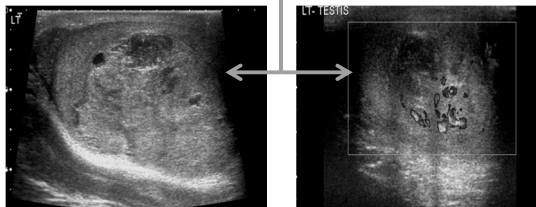
Embryonal cell; yolk sac

Half-life: 5-7 days

Excludes diagnosis seminoma

25 yo left testicular pain, palpable mass;
markers: AFP: 3639 HCG: 650.1

Hypoechoic, vascular mass



left orch: EC / YS / (-)LVI
3 days post – orch: HCG: 66.6; AFP 1655
CT CAP: NORMAL

S/P left orch: EC / YS / (- LVI); asymptomatic
CT scan CAP normal

	07/10/14 13:48	07/15/14 17:13
Transferrin Saturation Index		
EGFR African American	* >60	
EGFR Non-African American	* >60	
EGFR Comment	* (NOTE) ...	
Tumor Markers		
Alphafetoprotein	* ↑ 3439.0	* ↑ 1645.9
Beta-HCG	* ↑ 650.1	* ↑ 66.6
Beta-HCG, Tumor Marker		

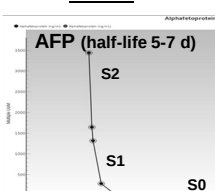
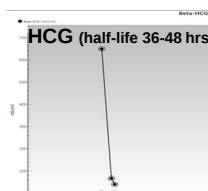
↑
orchietomy

S/P left orch: EC / YSI (-LVI); asymptomatic
CT scan CAP normal

AFP normalized in 2 months

	07/10/14 13:48	07/15/14 17:13	07/17/14 11:13	07/30/14 10:45	08/21/14 11:02	09/02/14 16:59	09/11/14 08:59	10/09/14 09:04
Transferrin Saturation Index								
EGFR African American	*	>80						
EGFR Non-African American	*	>80						
EGFR Comment	*	(NOTE)						
IGCCCG Risk Group								
Alpha-fetoprotein	* ↑ 3439.0	* ↑ 1645.9	* ↑ 1316.5	* ↑ 284.0	* ↑ 27.1	* ↑ 8.2	* 5.2	2.6
Beta-HCG	* ↑ 650.1	* ↑ 66.6	* ↑ 40.0	* <2.0	* <2.0	* <2.0	* <2.0	
Beta-HCG, Tumor Marker								

HCG normalized in 2 weeks



Serum Tumor Markers

IGCCCG Risk Group	Good S1	Intermediate S2	Poor S3
AFP	< 1000	1000-10,000	> 10,000
HCG	< 5000	5000-50,000	> 50,000
LDH	< 1.5x	1.5-10x	> 10x
Chemotherapy	BEPx3 EPx4	BEPx4	BEPx4

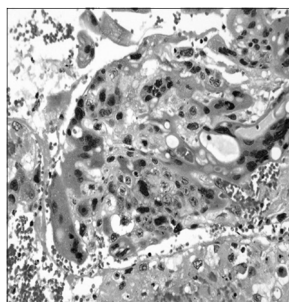
Chemotherapy regimen based on IGCCCG risk group
Marker status (S1-3) based on post-orchietomy nadir level

IGCCCG Risk Category

S Stage	LDH U/Liter	HCG (mIU/ml)	AFP (ng/ml)
S1	1-1.5 x ULN	<5,000	<1,000
S2	1.5-10 x ULN	5,000-50,000	1,000-10,000
S3	>10 x ULN	>50,000	>10,000

IGCCCG Risk	CTX	Visceral Mets	STM
Good	EP x 4; BEP x 3	pulmonary	S1
Intermediate	BEP x 4	non-pulmonary	S2
Poor	BEP x 4	non-pulmonary	S3

Choriocarcinoma

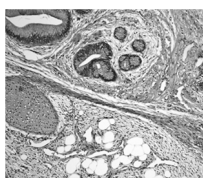


Choriocarcinoma not adverse factor in mixed GCT

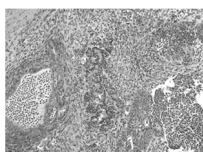
Pure choriocarcinoma
very high HCG
multiple pulmonary mets
r/o brain mets

Prognostic impact reflected in nadir post-orchietomy HCG level (IGCCCG risk)

Teratoma: Histology ≠ Biology



MATURE TERATOMA



IMMATURE TERATOMA

- Both histologically benign
no prognostic difference
- Unpredictable biology
growth
malignant transformation
- Chemoresistant
- Presence in 1° increases
probability of teratoma in RP

Management of Clinical Stage I NSGCT

Goals

- Low relapse rates
- Low treatment toxicity
- Few long-term treatment sequelae (toxicity, late relapse)

Options

- Surveillance
- Chemotherapy
- Bilateral Nerve-sparing RPLND

-patient selection
- proper execution of each treatment option !!!

Clinical Stage I NSGCT what is risk of relapse??

<u>Factors</u>	<u>Treatment</u>	<u>Relapse</u>	<u>NED (%)</u>
→ No LVI (I-A)	observe	~15%	~99%
LVI, T1-4 (I-B)	observe	~45%	~99%
→ ↑STM, T1-4 (I-S)	observe or RPLND	~99%	~99%

Clinical Stage IS Elevated Serum Tumor Markers (STM)

Usually reflects systemic disease and patients should receive 1° chemotherapy

↑STM pre-RPLND is predictive for:

1. Systemic relapse (100%) in clinical stage I S (*J Urol* 152:111, 1994)
2. Relapse in low volume (pN1) RP disease (*J Clin Oncol* 19:2020, 2001)
3. Persistent NSGCT (↑STM) in high volume (pN2/3) RP disease (*Proc ASCO* 18:308A, 1999)

Clinical Stage I – II NSGCT Elevated Serum Tumor Markers (pre-RPLND) Usually reflects occult systemic disease

<u>Author, ref</u>	<u>Relapse Rate (%)</u>
Socinski et al: J Urol, 1988	60%
Rabanni et al: JCO, 2001	80%
Stephenson et al: JCO, 2005	72%

AVOID 1° RPLND
THESE PATIENTS SHOULD RECEIVE INDUCTION CTX

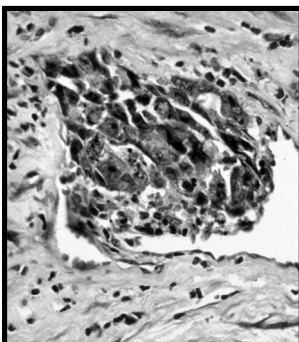
Clinical Stage I NSGCT Surveillance

Number of evaluable pts	2, 587
Patients with NED	2,169 (>98%)
Number of relapses (all pts)	759 (29%)
CS IA (Absence of LVI)	< 15%
Median time to relapse	7 (4-13) months

Vergouwe Y et al; JCO 21: 4092; 2003

- Curability of relapsed chemo-naïve patients
- Increased burden of therapy ?
- Compliance !!!

Embryonal Carcinoma and LVI

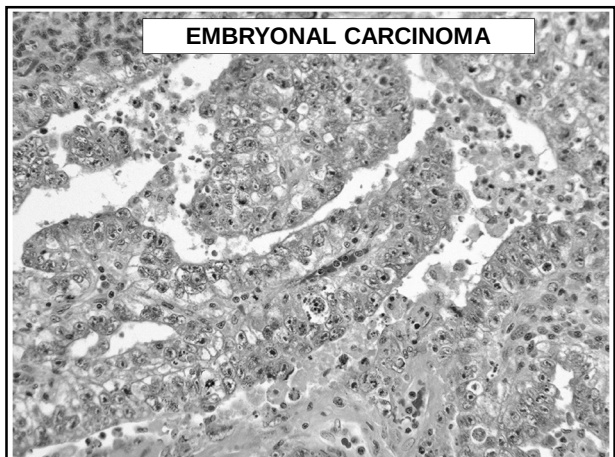


Embryonal carcinoma with LVI

predicts for relapse on surveillance or pN+ at RPLND

**NO ADVERSE
PROGNOSTIC IMPACT
IN ADVANCED NSGCT !!!**

EMBRYONAL CARCINOMA



Predictors of occult metastasis in Clinical Stage I NSGCT					
Table 2. Pooled Univariable Odds Ratios for Predictors of Occult Metastasis in Clinical Stage I NSGCT					
Predictor	Study References No.	No. of Patients	Patients With Characteristic (%)	OR	95% CI
Vascular invasion					
Venous, presence v absence	17, 19, 22, 33, 43, 47	1,007	42	4.7	2.5 to 8.5
Lymphatic, presence v absence	17, 19, 22, 43, 47	853	18	5.4	3.0 to 13
Venous or lymphatic, presence v absence	6, 19, 20, 23, 25, 26, 29, 32, 35, 39, 48, 50, 55	1,364	36	2.2	1.4 to 3.6
Histology of primary tumor					
Embryonal carcinoma					
Presence v absence	6, 17, 19, 26, 33, 43, 48, 50, 51	1505	85	2.9	2.0 to 4.4
> 50% v ≤ 50%	20, 39, 49, 50, 52				1.7 to 4.6
Yolk sac					
Presence v absence	6, 17, 19, 26, 32, 33, 35, 43, 52, 53	1,599	52	0.91	0.68 to 1.3
Mature teratoma					
Presence v absence	19, 26, 52, 53	434	45	0.48	0.27 to 0.74
Differentiated teratoma					
Presence v absence	17, 43	595	6	0.13	0.02 to 0.85
Pathologic stage of primary tumor					
pT3-4 v pT1	17, 29, 32, 33, 43, 59	1,066	22	2.6*	1.8 to 3.8
Size of primary tumor, T, cm					
>3 v ≤3	16, 19, 20, 22, 26	594	68	1.5	0.99 to 2.3
AFP serum level					
Elevated v normal	16, 20, 24, 26, 29, 33, 52, 53	990	40	0.94	0.59 to 1.5
HCG serum level					
Elevated v normal	16, 20, 22, 33, 52, 53	550	32	1.1	0.49 to 1.8
Patient age, years					
>30 v <30	16, 20, 22, 43, 53	683	41	1.6	1.2 to 2.4
MB-1 staining, % of cells					
>70 v ≤70	35, 39, 49	212	55	4.7	2.0 to 11

Abbreviations: NSGCT, nonseminomatous testicular germ cell tumor; OR, odds ratio; AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; MB-1, monoclonal antibody against human nuclear cell proliferation-associated antigen (Ki-67); RPLND, retroperitoneal lymph node dissection.
*Heterogeneity of effect: surveillance studies: odds ratio, 2.1 (95% CI, 1.4 to 3.4); RPLND studies: odds ratio, 4.0 (95% CI, 2.5 to 7.7).
†Tumor size > 3 cm in references 16-19, 20, 22, 26, 29, 33, 52, 53; > 3.5 cm in reference 49.
‡Age > 29 years in references 16-19, 20, 22, 26, 29, 33, 52, 53; > 30 years in reference 49.

Vergouwe Y et al; JCO 21: 4092; 2003

Stage I NSGCT Active Surveillance Time to Relapse		
	IA	IB
	NSGCT LVI -	NSGCT LVI +
	n = 935	n = 183
relapse	132 (14%)	81 (44%)
<12 mo	95 (72%)	73 (90%)
<24 mo	118 (89%)	77 (95%)
<36 mo	124 (93%)	79 (98%)
>36 mo	8 (7%)	2 (2%)

Kollmannsberger et al; JCO 33:51; 2014

Stage I NSGCT Active Surveillance Initial Detection of Relapses		
	IA	IB
	NSGCT LVI -	NSGCT LVI +
	n = 935	n = 183
relapses	132 (14%)	81 (44%)
Method 1 st detection		
Abd CT	63 (48%)	31 (38%)
markers	54 (41%)	49 (61%)
N/A	12 (9%)	

Kollmannsberger et al; JCO 33:51; 2014

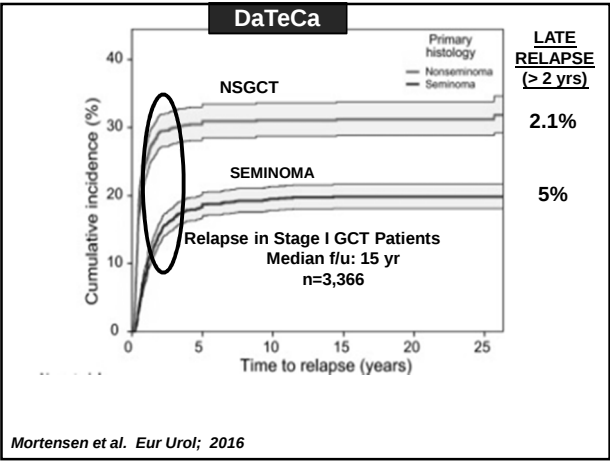


Table 1 Clinical Stage IA, NSGCT: Active Surveillance					
Year (at month intervals)					
	1	2	3	4	5
H&P and markers ^a	Every 2 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Annually
Abdominal/pelvic CT	Every 4-6 mo	Every 6-12 mo	Annually	-	-
Chest x-ray ^b	At mo 4 and 12	Annually	Annually	Annually	Annually

Table 2 Clinical Stage IB, NSGCT: Active Surveillance					
Year (at month intervals)					
	1	2	3	4	5
H&P and markers ^a	Every 2 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Annually
Abdominal/pelvic CT	Every 4 mo	Every 4-6 mo	Every 6 mo	Annually	-
Chest x-ray ^b	Every 2 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Annually

Table 7 Clinical Stage I Seminoma: Surveillance After Orchiectomy					
Year (at month intervals)					
	1	2	3	4	5
H&P ^{a,b}	Every 3-6 mo	Every 6-12 mo	Every 6-12 mo	Annually	Annually
Abdominal/pelvic CT	At 3, 6, and 12 mo	Every 6-12 mo	Every 6-12 mo	Every 12-24 mo	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients				

ESMO		NSGCT		Year									
stage	Strategy	Relapse rate		1	2 ^a	3	4	5 ^b	6 to 10 ^b				
I	Surveillance	Low risk: ≤ 20%	exam/ markers ^a	12x	4x	3x	2x	2x	2 ^a				
		High risk: ≥ 50%	chest X-ray	7x	4x	3x	2x	2x	2 ^a				
	Chemotherapy	≤ 3%	CT abdomen	2x	1x	-	-	-	2 ^a				
			exam/ markers ^a	5x	3x	2x	2x	2x	2 ^a				
			chest X-ray	3x	1x	1x	1x	1x	2 ^a				
			CT abdomen	1x	-	-	-	-	2 ^a				

EAU		Year				
		1	2	3	4-5	
Physical examination	Four times	Four times	Four times	Four times	Once/yr	
Tumour markers	Four times	Four times	Four times	Four times	Once/yr	
Plain radiography of the chest	Twice	Twice	Twice	Twice	Twice	
Abdominopelvic computed tomography	Twice (at 3 and 12 mo)	Once (at 24 mo)	Once (at 36 mo)			

DaTeCa		Table 4. Suggestion for a Follow-Up Program for Patients With Stage I NSGCT									
		Month									
Program Element		1	2	3	4	5	6	7	8	9	10
CT scan		x	x	x	x	x	x	x	x	x	x
Tumor markers		x	x	x	x	x	x	x	x	x	x
Physical examination		x	x	x	x	x	x	x	x	x	x
Free and total testosterone, LH, FSH		x	x	x	x	x	x	x	x	x	x

Abbreviations: CT, computed tomography; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NSGCT, nonseminoma germ cell cancer.

Scmolli et al. Ann Oncol; 2010 Albers et al. Eur Urol; 2015 Mortensen et al. Eur Urol; 2016

CT Chest: no role; CT pelvis: very low yield (selected cases)
Abdominal Imaging: CT vs MRI ??
Both require significant expertise
Far more experience with CT scans (↑↑ radiation exposure)
MRI: ↓↓↓ radiation exposure; ↑↑↑ \$\$
SWENOTECA has used for > 5 years
TRISST trial: 4 arm-double randomized noninferiority trial
3 CT vs 3 MRI (6, 18, 36 mo)
7 CT vs 7 MRI (6, 12, 18, 24, 36, 48, 60 mo)
MRI probably not ready for routine use in most centers now

Stage I NSGCT: Active Surveillance IGCCCG Risk of Relapses		
	NSGCT LVI + n = 183	NSGCT LVI - n = 935
relapses	81 (44%)	132 (14%)
IGCCCG risk		
Good	76 (94%)	116 (88%)
Int	3 (4%)	13 (10%)
Poor	2 (2%)	3 (2%)
STATUS		
NED	79 (98%)	126 (95%)
DOD	--	3 (2%)
Rx death	--	2 (2%)

Kollmannsberger et al; JCO 33:51; 2014

Stage I GCT Active Surveillance IGCCCG Risk of Relapses			
	NSGCT LVI + n = 183	NSGCT LVI - n = 935	SEMINOMA n = 1,344
relapses	81 (44%)	132 (14%)	173 (13%)
IGCCCG risk			
Good	76 (94%)	116 (88%)	171 (99%)
Int	3 (4%)	13 (10%)	2 (1%)
Poor	2 (2%)	3 (2%)	--
STATUS			
NED	79 (98%)	126 (95%)	171 (99%)
DOD	--	3 (2%)	--
Rx death	--	2 (2%)	1 (<1%)

Kollmannsberger et al; JCO 33:51; 2014

Clinical Stage I NSGCT Surveillance	
Advantages Avoids overtreatment in: ~ 70% pts IA ~ 85%-88% IB ~ 50%	Disadvantages Higher risk relapse than with CTX or RPLND Long-term access to medical care ↑ burden therapy with relapse ? Serial RP imaging (CT scans) Compliance
Optimal candidates : Compliant CS IA (no LVI)	

Clinical Stage I NSGCT Risk Adapted Chemotherapy					
Author	Risk factor	Regimen	No.	Relapse	Median f/u (mo)
Pont	VI	BEP X 2	74	2 (2%)	79
Cullen	LVI, EC YS	BEP X 2	114	2 (2%)	48
Böhlen	LVI, EC, pT2+	BEP X 2 PVB X 2	58	1 (2%)	93
Maroto-Rey	LVI, EC	BEP X 2	231	3 (1%)	36
Klepp	LVI	BEP X 2	32	1 (3%)	40

SWENOTECA : BEP x 1						
Risk group	No. of patients	Median age (range), years	Median follow-up (years)	Relapses		Time to relapse (years)
				No.	K-M RR (%)	
All	517	29 (15-71)	7.9	12	2.4	12 0.3-3.6
With LVI	258	29	8.0	8	3.2	1.1 0.3-3.6
Without LVI	255	30	7.9	4	1.6	1.2 0.9-1.8
LVI uncertain	4	30	6.1	0	0	

~10% high risk NSGCT have teratoma in RP

Tandstad et al. Ann Oncol; 2014

Chemotherapy (BEP)	
Acute Toxicity	Late &/or Permanent Sequelae
Myelosuppression Nausea & vomiting Alopecia Stomatitis Thromboembolic events Deaths <u>Toxicity</u> Grade 1 or 2 ~ 50% Grade 3 or 4 ~ 8% - 15%	Nephrotoxicity Neurotoxicity ototoxicity peripheral neuropathy Raynaud's phenomenon Hypogonadism Infertility Cardiac toxicity Metabolic Syndrome Second malignancies

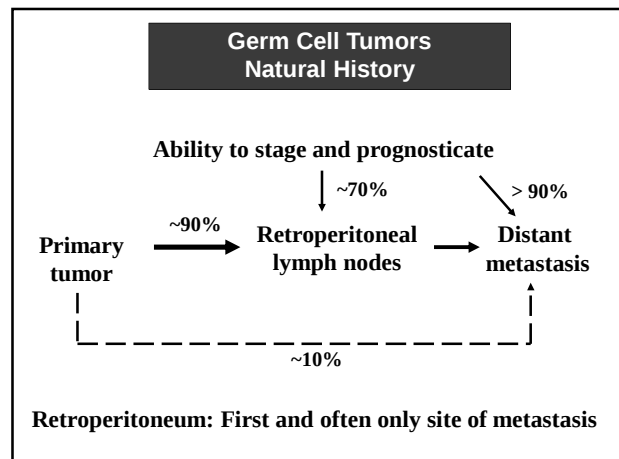
Clinical Stage I NSGCT Chemotherapy	
Advantages	Disadvantages
↓ risk of relapse (<3%) Need for tertiary center less compelling	Overtreatment in ~ 70% pts ~ 85% - 88% IA pts ~50% IB pts Short/ long-term sequelae ↑ risk CVD/ 2nd malignancies <u>Doesn't treat teratoma</u> Late relapse Requires serial RP imaging
Assumes that late toxicity not significant issue Assumes that <u>teratoma</u> is not a serious consideration	

Teratoma in Retroperitoneum			
	Institution	Pts	Teratoma in RP
CS I	MSKCC	37	4 (9%)
CS I, EC only	MSKCC	26	2 (8%)
Clinical I-IIA	Indiana	117 (N+)	37 (32%)
Clinical I-IIA	MSKCC	118 (N+)	25 (21%)

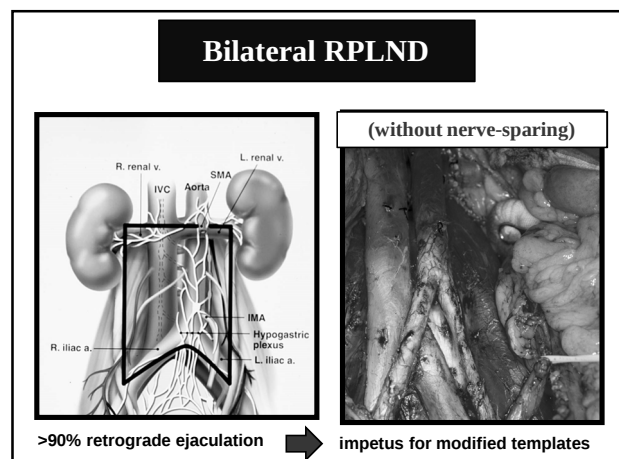
~ 10% of chemo treated CS I have untreated teratoma in RP

Teratoma occurs in metastasis even if none in 1^o

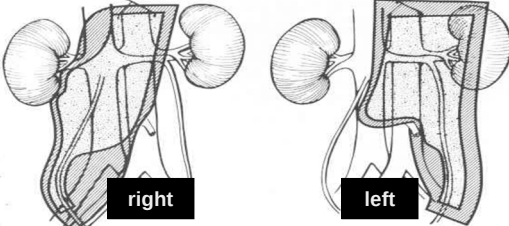
Teratoma cannot be reliably excluded



RPLND
RPLND remains a critical component in the management of selected patients with GCT Properly performed, RPLND is both a staging and therapeutic procedure, but it should <u>ALWAYS</u> be done with <u>THERAPEUTIC INTENT</u> Despite effective cisplatin-based chemotherapy, the potential consequences of untreated RP metastasis: late relapse re-operative surgery somatic transformation of teratoma INFERIOR SURVIVAL



Modified Template
Seminars in Urology 2: 264, 1984



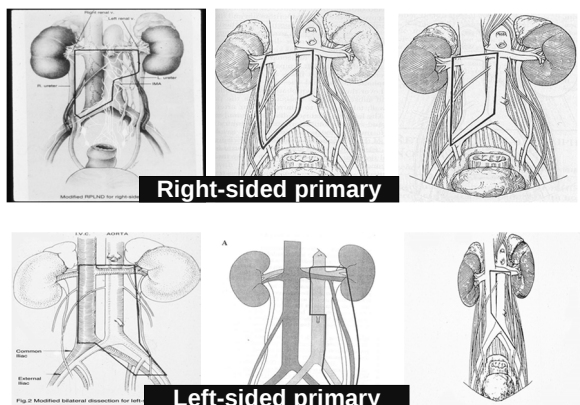
right left

Avoid dissection in areas thought to be at low (< 10%) risk for disease

Modified RPLND Templates

- Lange PH et al; Sem Urol, 1984
- Fossa SD et al; Eur Urol 1984
- Pizzocaro G et al; J Urol 1985
- Weissbach L et al; J Urol 1987
- Sherlog A et al; Urology 1989
- Richie J et al; J Urol 1990
- Donohue J et al; J Urol 1993
- Holtl L et al; Urology 2002

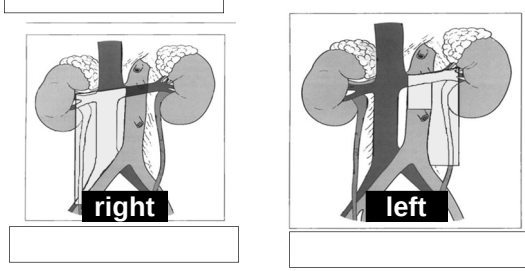
Modified RPLND Templates



Right-sided primary

Left-sided primary

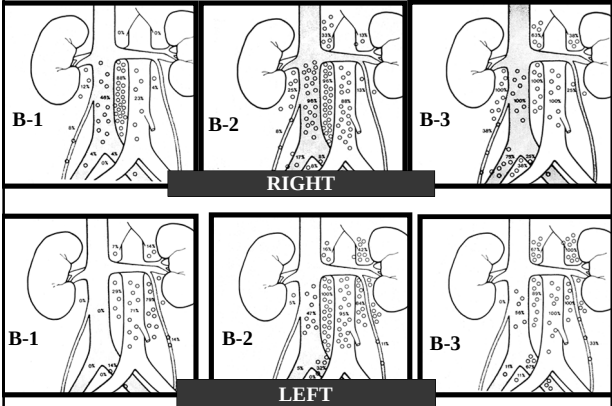
Modified RPLND Templates
Avoid contralateral dissection



right left

Avoid surgery in areas thought to be at low risk for disease
How was risk determined??

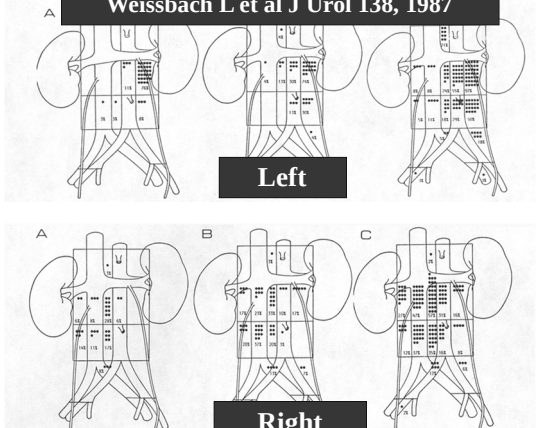
Donohue J et al, J Urol 128, 1982



B-1 B-2 B-3 RIGHT

B-1 B-2 B-3 LEFT

Weissbach L et al J Urol 138, 1987



A B C Left

A B C Right

Mapping Studies: Underestimate Retroperitoneal Disease

cannot assess incidence of unresected RP disease

1. Without adequate clinical follow-up

author, yr	no.	follow-up
Whitmore, 1973	283	none
Donohue, 1982	104	none
Weissbach, 1987	214	22 mo. pN0 (I) 42-44 mo. pN+ (II)

2. In patients who received postoperative chemotherapy

Weissbach study: PSII patients: PVB x 2 vs PVB x 4

BILATERAL

RPLND

≠

MODIFIED

•Extra-template disease for 5 Templates
 1° RPLND right: 2%- 28%; left: 4%- 25%
 PC-RPLND right: 4%-32%; left 11%-32%
 Eggener et al. J Urol ;2007; Carver et al JCO; 2007

Late Relapse
 Baniel et al. J Urol; 1995

Redo- RPLND: ~40% extra-template
 McKiernan et al; Urol; 2003
 Pedrosa J et al; J Urol; 2014

Impetus for Modified Templates: > 90% retrograde ejaculation

Late Relapse of Testicular Cancer Clinical Presentation

SITES OF LR

# of sites	Baniel (n=81)	George (n=83)	Sheinfeld (n=143)	Dieckmann* (n=122)
RP	43 (53%)	39 (47%)	118(83%)	71 (58%)
lung	19 (23%)	21 (25%)	28(19%)	8 (7%)
mediastinum	10 (12%)	8 (10%)	16(11%)	14 12%)
neck	8 (10%)	7 (8%)	13(10%)	10 (8%)

Baniel et al JCO 1995; Geldart et al BJUI 2006; Dieckmann et al J Urol 2005;
 Ravi et al BJUI 2003; George et al JCO 2003; Sheinfeld AAGUS 2018

Somatic Transformation of Teratoma

Definition: Components of teratoma that histologically resemble a somatic malignancy. (e.g., PNET, enteric adenocarcinoma, rhabdomyosarcoma)

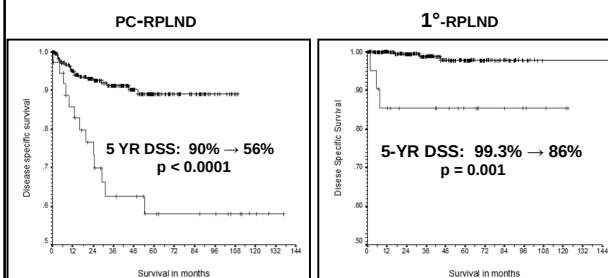
1° RPLND	0.4%
PC – RPLND	3%
Redo RPLND	18%
Late Relapse	21%

LR: 8-10X increased incidence compared to PC-RPLND
 ~12% in surveillance failures (no prior CTX)

REDO RPLND: 6-8X increased incidence

REOPERATIVE RETROPERITONEAL SURGERY FOR NONSEMINOMATOUS GERM CELL TUMOR: CLINICAL PRESENTATION, PATTERNS OF RECURRENCE, AND OUTCOME

JAMES M. MCKIERNAN, ROBERT J. MOTZER, DEAN F. BAJORIN, JENNIFER BACIK, GEORGE J. BOSL, and JOEL SHEINFELD



Redo surgery is an independent adverse variable

Chemotherapy will not compensate for suboptimal surgery

UROLOGY 62 (4), 2003

REOPERATIVE RETROPERITONEAL SURGERY FOR NONSEMINOMATOUS GERM CELL TUMOR: CLINICAL PRESENTATION, PATTERNS OF RECURRENCE, AND OUTCOME

JAMES M. MCKIERNAN, ROBERT J. MOTZER, DEAN F. BAJORIN, JENNIFER BACIK, GEORGE J. BOSL, and JOEL SHEINFELD

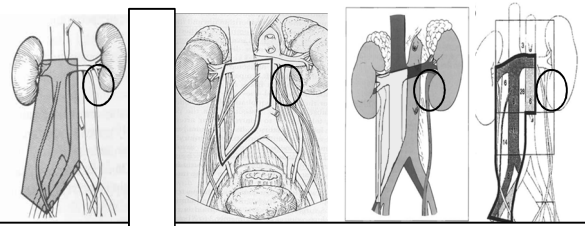
- Late relapse > 50%
 - Pathology
 teratoma: at initial RPLND - 54%; at redo-RPLND - 56%
 somatic transformation of teratoma at redo: 20%
 - Increased burden of therapy
 additional chemotherapy
 adjunctive procedures
- | | 1° RPLND | PC-RPLND |
|-------------------------|----------|----------|
| Redo after | | |
| additional chemotherapy | 86% | 50% |
| adjunctive procedures | 63% | 71% |
- Extra-template relapse ~ 40%
 (para-aortic most common)

UROLOGY 62 (4), 2003

Paraortic Lymph Nodes: Exposure and Technical Demands



Right Modified RPLND Templates



paraortic nodes not included

1° RPLND Extra-Template Disease for 5* Templates

Egger SE et al, J Urol 177, 937; 2007

RIGHT	LEFT
2% - 28%	4% - 25%

increases with clinical and pathological stage

Histologic distribution of extra-template disease virtually identical to in-template disease

*

Foster RS BJU Int 94, 2004	Weissbach L J Urol 138, 1987
Janetschek G Urology 55, 2000	Nelson JB Urology 54, 1999
Sheinfeld J Campbell's Urology 2005	

Negative Ipsilateral Nodes Contralateral Disease Only

Laterality	Right	Left
Egger	3%	5%
Weissbach	3%	5%
Leibovitch	6%	3%

Egger S et al, J Urol, 2007
Weissbach L et al, J Urol 138, 1987
Leibovich BC et al, J Urol 167: 683A, 2002

Consequences of Missed Nodes during Retroperitoneal Lymph Node Dissection and How to Avoid Them

Giorgio Pizzocaro*, Andrea Guarneri
University of Milano, S. Giuseppe Hospital, Urologic Clinic 2nd, Milano, Italy

Table 1 - Distribution of retroperitoneal lymph node metastases in pathologic stage IIA disease (sum of templates in Donohue et al [11] and Weissbach and Boedfeld [12])

Anatomic sites	Right side (92 patients)	Left side (75 patients)
Paracaval	21 (23%)	-
Precaval	37 (40%)	2' (2.7%)
Interaortocaval	55 (60%)	8 (11%)
Para-aortic	12 (13%)	24 (32%)
Right iliac	6 (6.5%)	67 (89%)
Common	8 (9%)	-
External	1' (1%)	-
Left iliac	3 (3%)	3 (4%)
Hilar/suprahilar	2' (2%)	3 (4%)

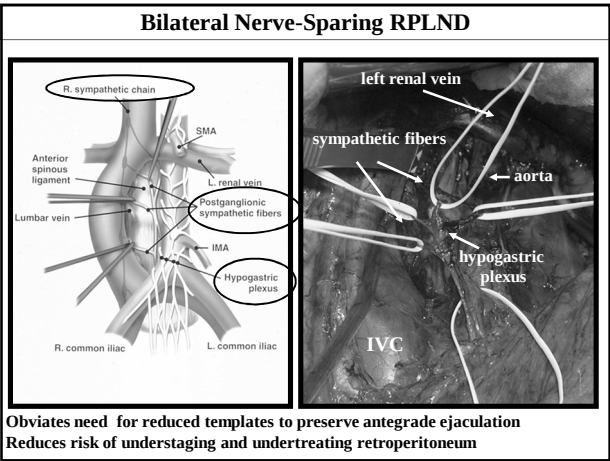
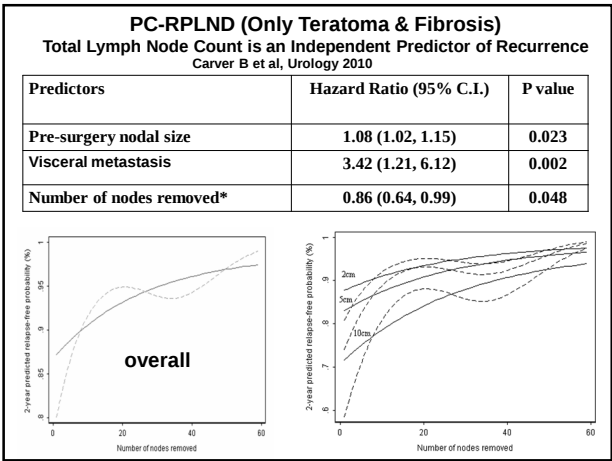
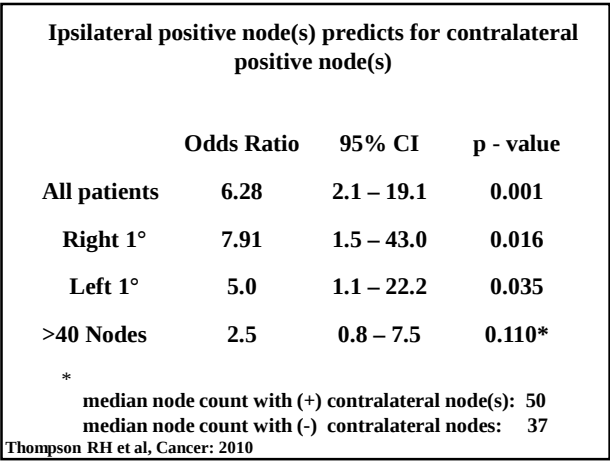
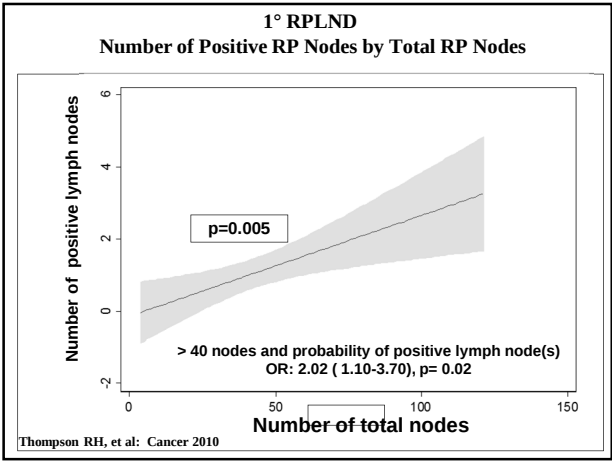
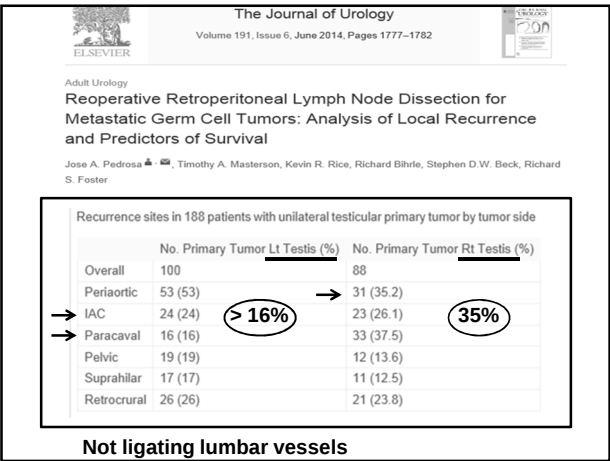
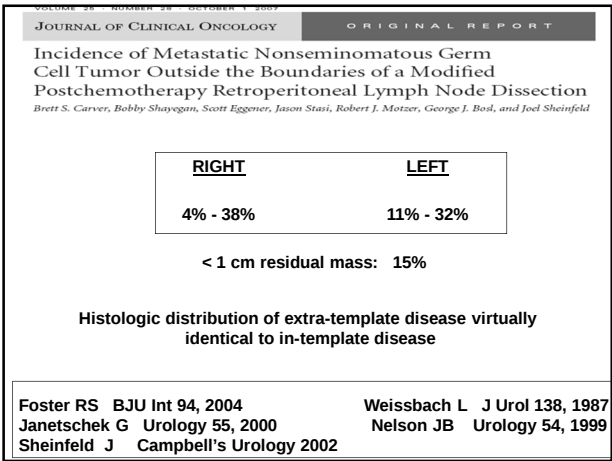
* Refers to Weissbach and Boedfeld [12] only.

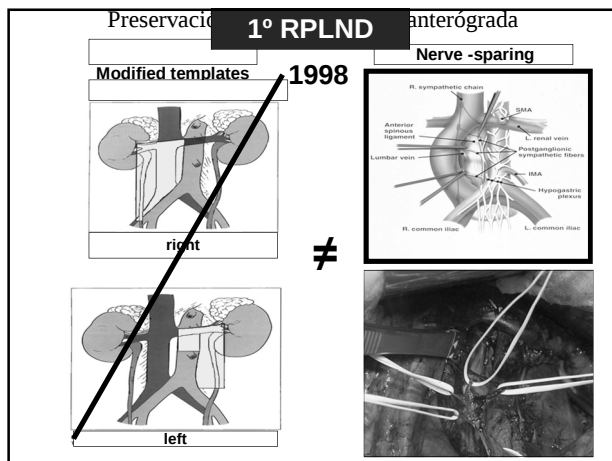
Consequences of Missed Nodes during Retroperitoneal Lymph Node Dissection and How to Avoid Them

Giorgio Pizzocaro*, Andrea Guarneri

4. Conclusions

The only conclusion is that landing zones for retroperitoneal lymph node metastases are too scattered to design a restricted template that will allow radical RPLND and an easy nerve-sparing technique to maintain antegrade ejaculation. If a restricted template is used, missed nodes are to be expected, and extratemplate metastases are not the fault of the template but a responsibility of the surgeon. We have also to bear clearly in mind that chemotherapy is not a panacea for missed or recurrent nodal metastases (memento teratoma) and that prospective nerve-sparing surgery is not only technically demanding but is also safer than templates.





1° RPLND and Clinical Outcome Over Time

Stephenson AJ et al, JCO 2005; 23: 2781-8

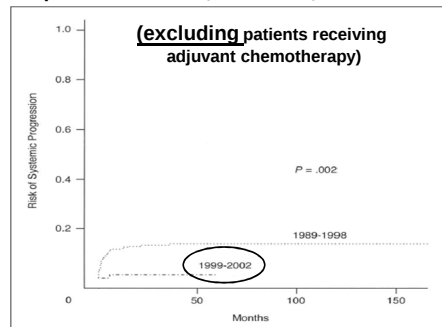
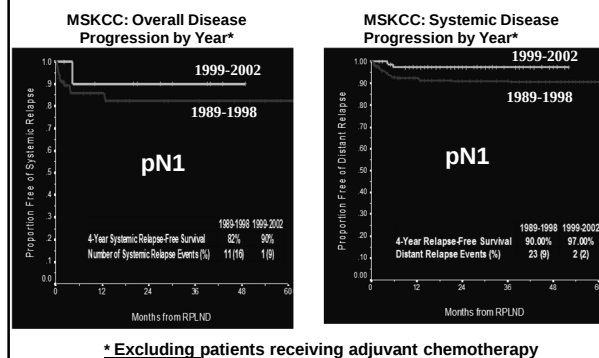


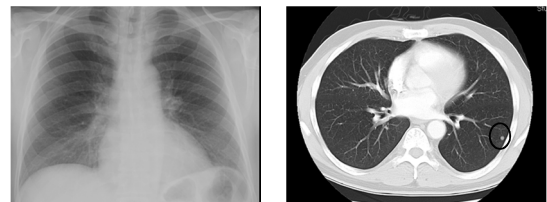
Fig 2. Competing risk analysis of the risk of systemic progression after retroperitoneal lymph node dissection (RPLND) for patients not receiving adjuvant chemotherapy, stratified by RPLND year before and after 1999.

Changes in Clinical Outcome Over Time

Stephenson AJ et al, JCO 2005; 23: 2781-8



Detecting Occult Systemic Disease



Normal post-orchietomy AFP and/or HCG

exclude IS and IIA (S1): ↑ AFP and/or HCG usually reflects occult systemic disease

Davis B et al; J Urol 152: 111,1994

Sheinfeld J et al; Proc ASCO, 1999

Rabbani F et al; J Clin Oncol 19: 2020, 2001

Extra - template and/or Contralateral GCT in the RP

RP mapping studies always underestimate RP disease

Ipsilateral disease predicts for contralateral GCT

Thompson et al, Cancer 2010; Donohue et al, J Urol 1982

Variable potential for unresected RP disease depending on template

Eggner et al, J Urol 2007; Carver et al, JCO 2007

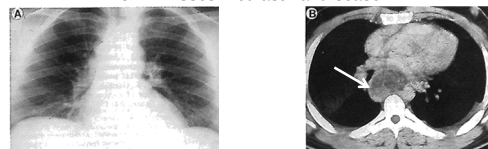
MSKCC: improved clinical outcomes for low-stage and PC - RPLND since modified templates abandoned (independent variable)

Stephenson et al, JCO 2005; Carver et al, JCO 2007

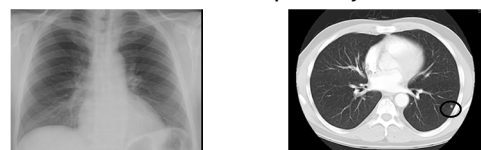
Clinical Stage I and II NSGCT

Improved Chest Staging with CT vs CXR

CXR misses mediastinal disease

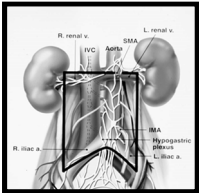


CXR misses small pulmonary nodules

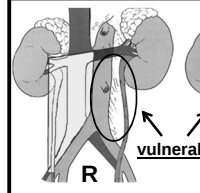


PRIMARY RPLND NOT INDICATED IN THESE CASES

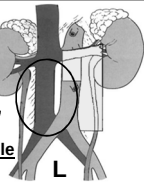
BILATERAL



1° RPLND



MODIFIED



≠

•Extra-template disease for 5 Templates
Right: 2%- 28%; left: 4%- 25%
Eggerer et al. J Urol ;2007

•Late Relapse
Baniel et al. J Urol; 1995

•Redo RPLND: 40% extra-template
Impetus for Modified Templates: > 90% retrograde ejaculation
McKiernan et al; Urol; 2003

Low Stage NSGCT

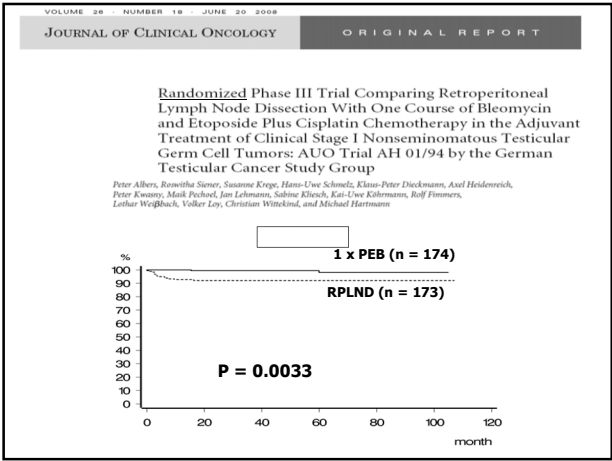
RPLND: bilateral, nerve-sparing

Performed with therapeutic intent: controlled RP... reduces chemotherapy burden (acute and long-term toxicity)

With more stringent selection criteria increased proportion of pathologic stage II with pN1 (rarely need chemotherapy)

RP histology has remained constant (> 20% teratoma in pN+; 10% CS IB with unresected teratoma if observed or treated with CTX) and risk for late relapse

Significant decrease in systemic relapse rates(<10%) with improved selection criteria.... and bilateral RPLND



VOLUME 26 : NUMBER 16 : JUNE 20 2008

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase III Trial Comparing Retroperitoneal Lymph Node Dissection With One Course of Bleomycin and Etoposide Plus Cisplatin Chemotherapy in the Adjuvant Treatment of Clinical Stage I Nonseminomatous Testicular Germ Cell Tumors: AUO Trial AH 01/94 by the German Testicular Cancer Study Group

Peter Albers, Renée Sier, Susanne Krage, Hans-Uwe Schmidt, Klaus-Peter Diekmann, Axel Heidenreich, Peter Kwiatky, Mark Pecher, Jan Lehmann, Sabine Klich, Kai-Uwe Köhmann, Rolf Fimmers, Lothar Wolfbach, Volker Loy, Christian Wittekind, and Michael Hartmann

Multi - institutional study: 60 centers

19 centers.....1 patient
11 centers.....2 patients
4 centers.....3 patients
1 center.....68 patients

Recent data demonstrating clear correlation between volume and outcome for complex procedures

CS I NSGCT

RPLND vs BEP x 1

randomized (ITT)
LVI ~ 43% (CS IB)
Median follow-up 4.7 years
35 patients excluded (protocol violation, seminoma – 7)
347 patients treated according to protocol (ATP)

BEP x1

n = 174

2 relapses

Ipsilateral RPLND

n = 173

32 (18%) pN+

141 (82%) pN0

BEP x2

IIA – 25
IIB – 6
IIC – 1

Observed

13 relapses
RP – 7
Scrotal – 2
Lung – 4

Albers et al JCO 2008

1° RPLND

Acute Morbidity

Wound infection

Pulmonary

Chylous ascites (<1%)

Lymphocele (<1%)

Pancreatic injury (<1%)

SBO (~1%)

Complications

major <5%

minor ~5%

Long-term Sequelae

Scar 100%

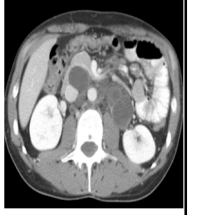
SBO (~1%)

Ventral hernia ~1%

Retrograde ejaculation <5%

Clinical Stage I NSGCT RPLND	
Advantages	Disadvantages
↓ risk relapse ↓ risk of needing CTX - removes teratoma ↓ risk late relapse - No need for serial RP imaging	- Overtreatment in (50% CS IB) ~ 10% - 20% receive postop CTX - Adjuvant: ≥ pN2 (decreasing) - Relapse (6%- 8%) - Major surgery: acute/ long-term morbidity - Retrograde ejaculation < 5% - REQUIRES EXPERIENCED SURGEON

Clinical Stage II NSGCT Management following 1° RPLND			
Pathologic Stage	Criteria	Relapse rate (%)	Management
pN0	All nodes -	<10%	Observe
pN1	< 2cm <5 + nodes No ENE	10%-15%	Observe if compliant
pN2/3	>2cm >6+ nodes ENE present ??	>40%	Adjuvant CTX preferable (B)EP x 2**
**RPLND with therapeutic intent, post-op evaluation: NED			
If rising STM, new pulmonary nodule -- INDUCTION CHEMOTHERAPY			

Clinical Stage II NSGCT (retroperitoneal disease only; +/- elevated STM) any pT/Tx; N1-3; M0; SX		
		
IIA < 2cm N1	IIB 2- 5 cm N2	IIC 5 cm N3

Clinical Stage II NSGCT Chemotherapy or RPLND as initial therapy
•Size of node(s) (Stage IIA, IIB, IIC) •Tumor marker (AFP / HCG) status (NADIR levels post-orchietomy) •Unifocal vs multifocal adenopathy •Symptoms (back, flank pain)
Which patients benefit from secondary (dual) therapy:
•Adjuvant chemotherapy after 1° RPLND •PC-RPLND after chemotherapy

Clinical Stage II NSGCT Initial therapy		
	RPLND	1° chemotherapy
<u>Clinical stage</u>	IIA selected IIB < 3 cm)	> 3 cm IIB all II C
<u>markers</u>	negative	elevated
<u># of nodes</u>	single	multiple
<u>symptoms</u>	absent	back/flank pain

Clinical Stage II NSGCT Rationale for Primary RPLND
Declining relapse rates and curative as single modality in most due to improved selection criteria
Removes chemoresistant GCT, particularly TERATOMA (20% - 30%)
More favorable long-term toxicity profile compared to chemotherapy
Serial CT imaging of abdomen unnecessary in follow-up
25% - 30% CS IIA are pN0
Optimal patients for Primary RPLND: CS IIA, small, unifocal IIB (<3 cm); <u>NORMAL STM</u>

Treatment and Outcome for Patients with IIA and IIB NSGCT

	1989-1998	1999-2002
Patients	181	71
Treatment		
RPLND	113 (62%)	23 (32%)
induction chemo	68 (38%)	48 (68%)
5 year RFS %	84	98
5 year DSS %	99	100

Stephenson AJ et al JCO 2007; 25:5597-5602

Improved Patient Selection ➡ Improved Clinical Outcomes

CT imaging of Chest
excluding patients with elevated STM
excluding CS IIB >3cm

- Elevated STM ($P < .0001$), independent predictor of progression
- Patients with elevated STM excluded; proportion of pN+: low-volume (pN1) disease increased by 24% (40% vs 64%)
- Progression-free survival improved from 83% to 96% ($p = .005$)
- Excluding patients with elevated STM from primary bilateral RPLND reduced extent of retroperitoneal disease and risk of relapse

Stephenson AJ et al, J Clin Oncol 2005; 23: 2781-8

Clinical Stage II NSGCT

Optimal patients for Induction Chemotherapy

- all CS IIC
- symptomatic, contralateral, multifocal, CS IIB >3 cm
- Any CS II (A-C) with elevated STM

IGCCCG Risk Category

S Stage	LDH U/Liter	HCG (mIU/ml)	AFP (ng/ml)
S1	1-1.5 x ULN	<5,000	<1,000
S2	1.5-10 x ULN	5,000-50,000	1,000-10,000
S3	>10 x ULN	>50,000	>10,000

IGCCCG Risk	CTX	Visceral Mets	STM
Good	EP x 4; BEP x 3	pulmonary	S1
Intermediate	BEP x 4	non-pulmonary	S2
Poor	BEP x 4	non-pulmonary	S3

Clinical Stage II NSGCT Summary

- Importance of patient selection:
 - chemotherapy
 - all IIC, multifocal; >3cm and /or symptomatic IIB
 - any IIA/B/C with elevated and / or rising markers
 - RPLND
 - NORMAL markers
 - IIA, <3cm unifocal, asymptomatic IIB
- Importance of optimal execution of selected treatment
 - RPLND with curative intent
 - Chemotherapy appropriate regimen according to IGCCCG criteria
- Subset of patients require dual therapy (optimal sequencing)
 - PC-RPLND all residual masses >1cm
 - adjuvant chemotherapy after primary RPLND: pN2/3, noncompliant pN1
- Adjuvant chemotherapy (B)EP x 2
 - post op patient MUST be NED;
 - if rising marker/ new nodule needs induction regimen

Take Home Messages

Delay in diagnosis continues to be a significant problem

A solid intratesticular solid mass is testicular cancer until proven otherwise

Scrotal sonography very useful: GCT's are usually hypoechoic, vascular lesion(s)

PET Scan has no role in initial evaluation of GCT

Elevated AFP excludes the diagnosis of seminoma despite histology of orchiectomy

Serum tumor markers that fail to normalize following orchiectomy usually reflect systemic disease and patients should receive 1° chemotherapy regardless of CT findings

Bilateral nerve-sparing RPLND reduces risk of understaging and undertreating the retroperitoneum

Advanced NSGCT
IGCCCG Risk Category



Pulmonary mets
GOOD RISK

Non-pulmonary mets (hepatic)
POOR RISK

IGCCCG Risk Category
Standard of Care

Table 1. The International Germ-Cell Cancer Collaborative Group prognostic grouping for seminoma and non-seminomatous germ-cell tumours

Parameter	Good	Intermediate	Poor
Seminoma			
α-fetoprotein	Normal	Normal	
HCG	Any	Any	
Lactate dehydrogenase	Any	Any	
Primary	Any	Any	
Other	No non-lung secondary tumours	No non-lung visceral secondary tumours	
% patients	90%	10%	
5-year survival	86%	72%	
Non-seminomatous germ-cell tumour			
α-fetoprotein	<1000	1000-10 000	>10 000
HCG	<5000	5000-50 000	>50 000
Lactate dehydrogenase	<1.5×ULN	1.5-10×ULN	>10×ULN
Primary	Testis/retroperitoneum	Testis/retroperitoneum	Mediastinal
Other	No non-lung secondary tumours	No non-lung secondary tumours	No non-lung secondary tumours
% patients	56%	28%	16%
5-year survival	92%	80%	48%

Good Risk
Visceral mets: pulmonary
Marker levels: S1
BEP x 3 or EP x 4

Intermediate/Poor Risk
Visceral mets: non-pulmonary
Marker levels: S2, S3
BEP x 4
VIP / TIP

HCG, human chorionic gonadotrophin.

PC - RPLND

Markers normalized
Residual mass > 1 cm

no controversy



PC-RPLND Histology				
Author, year	no.	fibrosis	teratoma	viable ca
Donohue, 1982	51	16 (31%)	16 (31%)	19 (37%)
Fossa, 1989	101	52 (51%)	37 (37%)	12 (12%)
Toner, 1990	122	57 (47%)	48 (38%)	17 (14%)
Aass,1991	173	85 (49%)	50 (25%)	38 (29%)
Steyerberg, 1995	556	250 (45%)	236 (42%)	70 13%
Stenning,1998	153	45 (29%)	85 (56%)	23 (15%)
Hendry, 2002	330	84 (25%)	218 (66%)	28 (8%)
Oldenburg, 2003	87	58 (67%)	23 (26%)	6 (7%)
Carver, 2005	428	214 (50%)	183 (43%)	31 (7%)
TOTAL	2001	861 (43%)	896 (45%)	244 (12%)

PC – RPLND Histology
Induction Chemotherapy

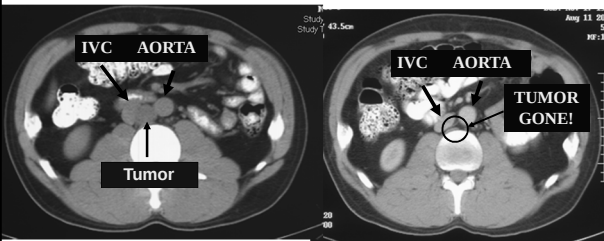
	<u>fibrosis</u>	<u>teratoma</u>	<u>viable ca</u>
Multiple series*	~ 50%	~ 40%	~ 10%

Incidence of viable ca has decreased over time

Controversy has centered on the patients with fibrosis, particularly if residual node(s) < 1 cm on post-chemo CT scan

*Donohue, 1987; Toner, 1990; Aass, 1991; Fossa, 1992; Steyerberg, 1995; Oldenburg, 2003; Sheinfeld, 2005

Postchemotherapy CT Scan < 1 cm



In general, the smaller the node, the greater the controversy

NSGCT
Observation following Chemotherapy

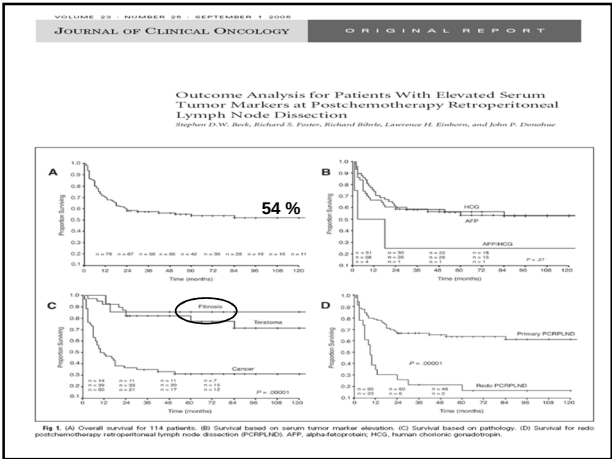
- 1) Assumption that surgery resulting in fibrosis is never therapeutic
- 2) Assumption that one can accurately predict fibrosis
- 3) Assumption that small foci of teratoma are “inert” or “benign”
- 4) Assumption that can achieve comparable patient outcomes with timely and appropriate treatment at relapse

Therapeutic Benefit of a “Negative” PC-RPLND
Pathologic Sample Error

Approximately 15% of patients will have a “negative” histology following PC-RPLND with elevated STM; yet ~ 90% will normalize their markers

The more extensive a “negative” PC-RPLND, the less likelihood of relapse

Molecular data ??



Clinical Outcome of Patients with Fibrosis/Necrosis at
Post-Chemotherapy Retroperitoneal Lymph Node Dissection for
Advanced Germ Cell Tumors

Roy Mano, Brett S. Carver, George J. Bosl, Robert J. Motzer, Dean F. Bajorin,
Darren R. Feldman and Joel Sheinfeld
Memorial Sloan Kettering Cancer Center, New York, NY

KM curves of recurrence free survival stratified by surgical templates

Residual mass < 1 cm
Observation vs PC RPLND

Most centers observe residual node(s) < 1 cm

Risk of relapse: for < 1cm ~ 7%*; for CR <5%

PC RPLND**
< 1 cm; teratoma 25%, viable ca 5%
< 0.5 cm; teratoma 16%; viable ca 4%

*IU, 2010
**MSKCC, 2006

NSGCT
Postchemotherapy Residual Masses < 1 cm

	no.	<u>fibrosis</u>	<u>teratoma</u>	<u>viable ca</u>
<u>0 - 5 mm</u>				
Multiple series*	119	95 (80%)	19 (16%)	5 (4%)
<u>5 - 10 mm</u>				
Multiple series*	130	85 (65%)	37 (29%)	8 (6%)

*Fossa, 1992; Oldenburg, 2003; Karellas, 2006

Postchemotherapy Histology Steyerberg Model of Predicting Necrosis

- Sum score (necrosis):
 - 9.78 + 8.58 • “teratoma-negative”
 - +8.70 • “AFP Normal”
 - +7.61 • “HCG normal”
 - +9.69 • ln (LDH_{st})
 - 2.83 • Sqrt (postsized)
 - +0.147 • shrinkage
- False negative
> 20%

Steyerberg EW et al. J Clin Oncol 16:269, 1998

Models Predicting Postchemotherapy Necrosis

Steyerberg EW et al; J Clin Oncol 1998
false negative > 20%

Albers P et al; J Urol 2004
accuracy 75%; sensitivity 52%; PPV 67%; NPV 77%
“clinically irrelevant model”

Toner G et al; J Clin Oncol 1990
accuracy 83%

PC – RPLND: Teratoma in Retroperitoneum

<u>Teratoma in 1° YES</u>	<u>no.</u>	<u>Teratoma in RP</u>
Beck, 2004	375	321 (86%)
Carver, 2006	224	150 (67%)
<u>Teratoma in 1° NO</u>		
Toner, 1990	75	25 (33%)
Beck, 2004	269	130 (48%)
Carver, 2006	308	85 (28%)
< 1 cm RP node	117	19 (16%)
1 -2 cm RP node	120	25 (21%)

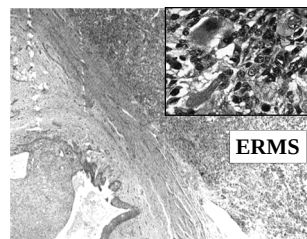
Predicting teratoma in RP

Carver et al, JCO 2007

	<u>Hazard ratio</u>	<u>95% C.I.</u>	<u>P-value</u>
IGCCCCG	0.61	0.35, 1.08	0.089
2 nd line chemo	0.51	0.26, 1.0	0.048
CT size pre-	0.77	0.7, 0.85	<0.005
CT size post-	1.6	1.4, 1.83	<0.005
<u>ORCHIECTOMY</u>			
teratoma	3.31	2.11, 5.21	<0.005
yolk sac	1.79	1.14, 2.83	0.012
embryonal ca	1.41	0.8, 2.5	0.2

Somatic-type Transformation of Teratoma: Higher incidence in LR and / or Redo RPLND

	<u>no. pts</u>	<u>TMT (%)</u>
1° RPLND	550	2 (0.4%)
PC - RPLND	532	18 (3%)
Redo RPLND	56	10 (18%)
Late Relapse	69	14 (20%)



TERATOMA WITH SOMATIC-TYPE TRANSFORMATION (2° somatic malignancy)

Unresected teratoma;
some YS

Definition: Components of teratoma that histologically resemble a somatic malignancy. (e.g., PNET, enteric adenocarcinoma, rhabdomyosarcoma)

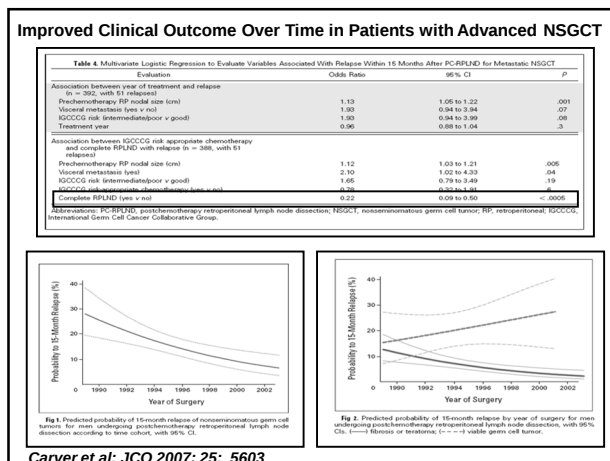
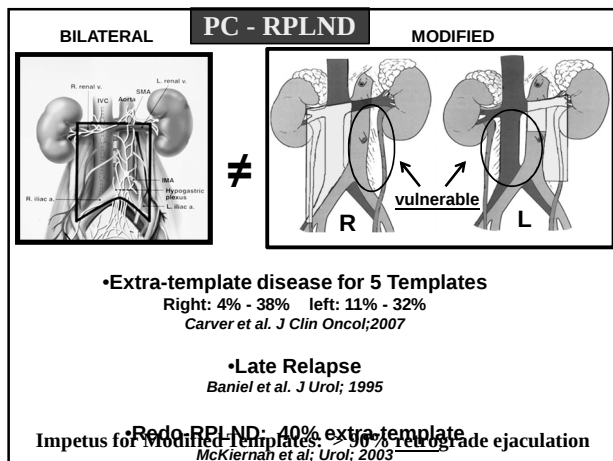
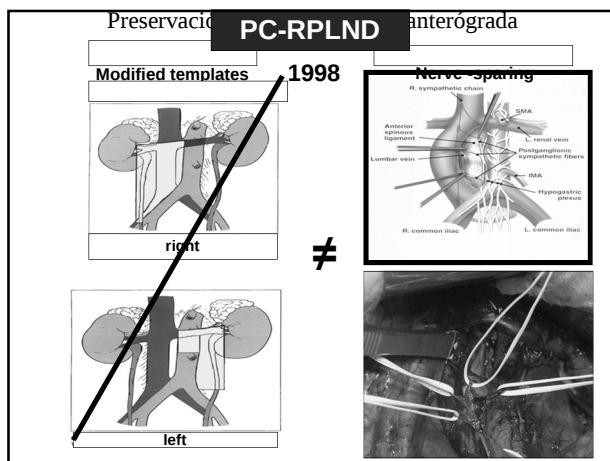
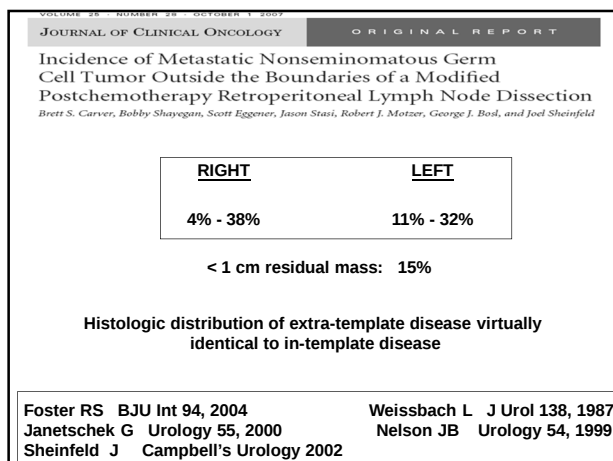
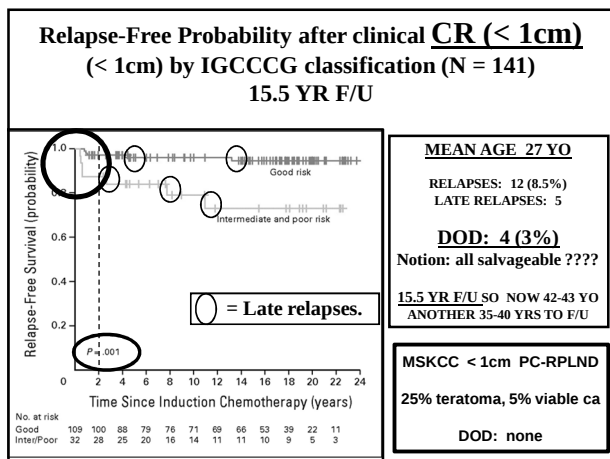
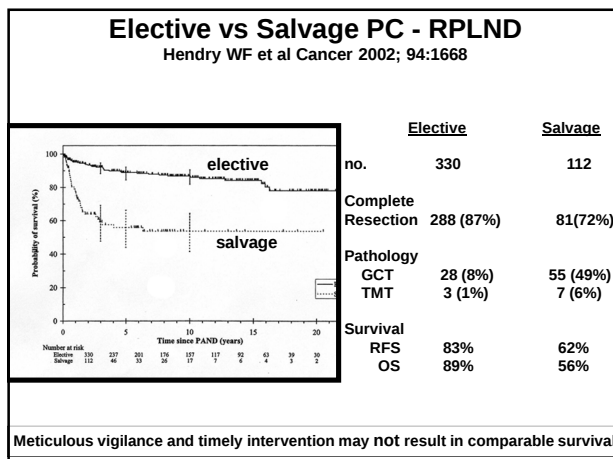
Somatic Transformation of Teratoma

Definition: Components of teratoma that histologically resemble a somatic malignancy. (e.g., PNET, enteric adenocarcinoma, rhabdomyosarcoma)

1° RPLND	0.4%
PC – RPLND	3%
Redo RPLND	18%
Late Relapse	20%

LR: 8-10X increased incidence compared to PC-RPLND
~12% in surveillance failures (no prior CTX)

REDO RPLND: 6-8X increased incidence



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JOURNAL OF CLINICAL ONCOLOGY EDITORIAL

Weighing Risks and Benefits of Postchemotherapy Retroperitoneal Lymph Node Dissection: Not So Easy

George J. Bosl and Robert J. Motzer, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

- Both standard options; need to account for short, intermediate and long-term risks
- Surveillance: fewer operations, less perioperative morbidity, less need expert surgeons long-term imaging RP account for teratoma in 1%; ?? limit to good risk
- PC-RPLND: reduce risk of RP as site for (late) relapse; TMT reduce risk for salvage chemotherapy reduce need for RP imaging

Best outcomes if managed in high volume centers

Post Chemotherapy Surgery: More chemo if viable GCT is found?

	Primary Chemo (%) N=27	Salvage Chemo (%) N=25
<u>Post-Op Chemo</u>		
NED	19 (70)	9 (36)
<u>No Post-Op Chemo</u>	N=7	N=28
NED	0 (0)	12 (43)

ANSWER:

1. If first chemo → YES.
2. If 2nd chemo → NO

Fox et al, JCO 1993

Viable Malignant Cells After Primary Chemotherapy for Disseminated Nonseminomatous Germ Cell Tumors: Prognostic Factors and Role of Postoperative Chemotherapy—Results From an International Study Group

By Karim Fizazi, Sergei Tjuland, Roberto Salazar, José R. Gascón-Llach, Jeanine Bouay, David Rognon, Corinne Beckmann, Arthur Gori, André Fléchon, Johann S. de Bono, Sally Shering, Alan Horwich, Jörg Pient, Peter Albers, Ugo De Giorgi, Mark Bower, Anselmi Salazar, Giorgio Pizzocaro, Jorge Aparicio, Craig R. Nichols, Christine Theodore, Jörg Thomas Hartmann, Hans-Joachim Schmoll, Stanley B. Kroyer, Stéphane Culine, Jean-Pierre Droz, and Cedric Hahn

Viable Cells After Chemotherapy for NSGCT

Favorable prognostic variables:

- < 10% viable cells (p = 0.001)
- IGCCCG good risk (p = 0.01)
- complete resection (p < 0.001)

Fig 1. Overall survival of patients with postchemotherapy viable malignant cells from NSGCTs according to their allocation into risk groups.

sCR1 study recently validated in sCR2 study: Annals of Oncology, 2008
"Complete resection of residual masses should be rigorously pursued"

"Fox et al, 1993 "incomplete resection portends a very poor prognosis"

PC-RPLND and Adjunctive Procedures

Left colectomy, recurrent hilum spleen
Splenectomy, distal pancreatectomy

Left colectomy
Left nephrectomy

Resect all residual mass(es) (Histologic discordance ~ 30%)

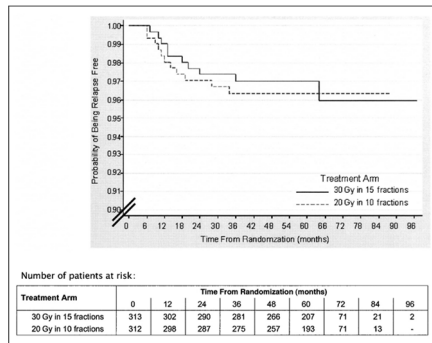
Author, year	no.	% discordance
Mandelbaum, 1983	24	29%
Tiffany, 1986	23	35%
Steyerberg, 1997	215	36%
Hartmann, 1997	27	30%
Tognini, 1998	143	31%
McGuire, 2003	105	38%
Shayegan, 2006	130	34%
Beese, 2009	52	27%

SEMINOMA

(B)EP is standard treatment for CS II B/C and CS III.

What about CS I and CS IIA seminoma?

Radiation for Stage I Seminoma: 20Gy = 30Gy



Jones, W. G. et al. J Clin Oncol; 23:1200-1208 2005

Stage I Seminoma: Dog-Leg vs. PA-only (Fossa, JCO, 1999)

	PA-Strip N=236	Dog-Leg N = 242	P Value
Relapses	9	9	NS
Pelvic Relapses	4 (2%)	0	0.04
RFS	96%	96.6%	NS
OS at 3-years	99.3%	100%	NS

No difference in RFS or OS but pelvic relapses ↑ with PA-only.

Either approach is reasonable but if PA-only, need to get f/u pelvic CTs; • MSKCC prefers DL

Stage I – Radiation Considerations

- Relapse rate = 4%
- Dose
 - No benefit of 30Gy over 20Gy (Jones et al., JCO)
 - Standard is 20 – 25.5Gy
- Port
 - Dog-leg (DL) vs. Retroperitoneal-only (RP)
 - No difference in overall relapse rate (4%) but higher pelvic relapse rate (2% vs. 0%). CT pelvis needed for RP-only port in f/u.
 - No prophylactic mediastinal or left SCL XRT
- Late toxicities
 - Secondary malignancies (2-fold increase, esp. gastric, pancreatic, bladder, sigmoid, rectal, anal) but 50% outside radiation port (???)

CS 1 Seminoma: XRT

Stage	RT	Relapse (%)
I	20-25 Gy	4%

After RT, Increased cancer risk exists.

1. CA colon, stomach, pancreas, others.
Colon: RR 1.9; Pancreas: RR 3.8; Stomach: RR 4.1.
2. Long latency.
(Travis et al. JNCI 97: 1354, 2005)

Risk also increased after chemotherapy.

Stage I Seminoma – Surveillance

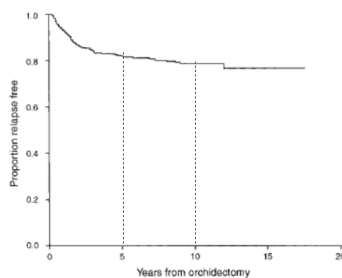


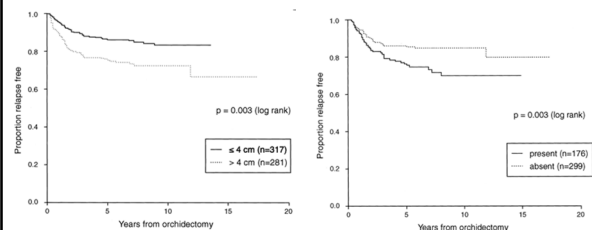
Fig 1. Relapse-free rate for all cases from date of orchidectomy.

- 83% relapse-free at 5-yrs
- 79% relapse-free at 10-yrs
- 69% of relapses occurred <2 yrs
- 7% of relapses occurred >6 yrs
- At relapse, most require chemo, some eligible for XRT

Warde JCO 2002

Stage I Seminoma – Surveillance

Tumor Size and Rete Testis involvement are risk factors for relapse



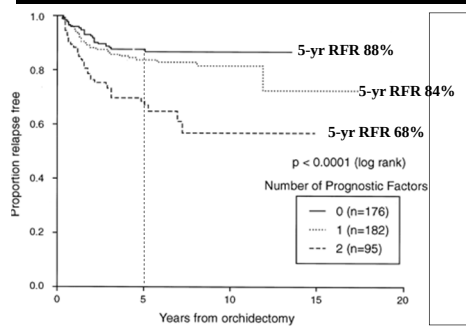
Tumor Size > 4cm

Rete Testis Involvement

Word of caution: Rete testis involvement not validated

Warde JCO 2002

Stage I Seminoma - Surveillance



Prediction model for relapse using combination of tumor size and rete testis +

Word of caution: Rete testis involvement not validated

Warde JCO 2002

Clinical Stage I Seminoma

(http://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf)

1. **Surveillance.** Now recommended by most guidelines.

2. **Radiation Therapy—CS I.**

Still in NCCN Guidelines. ~4-5% relapse.

****Must discuss late cancer risks with patient.**

Patients who relapse will receive BOTH RT and Chemotherapy

∴ Excess **Combined** Risk of Second Cancer + CVD.

3. **Risk Adapted Carboplatin.**

Most don't need it. 85% cured after orchidectomy.

Carboplatin in CS I Seminoma

Oliver et al, Lancet 2005; Oliver et al JCO, 2011

	RT	Carboplatin x 1
Patients	573	904
Relapse Free Rates	96%	94.7%
TOXICITY		
Low platelets		
Gr 1-2	2%	12%
Gr 3-4	0%	4%

Lethargy/ Back to Work 20 Gy = Carbo Carbo < 30 Gy

Clinical Stage IIA/B(<3 cm) Seminoma

Stage	RT	Relapse (%)
IIA/B (<3 cm)	30 Gy	10%-20%

1. **Radiation Therapy.** Remains a standard of care.

HOWEVER, Must discuss late cancer risks.

~10%-20% relapse after RT

∴ Those who relapse will have had **BOTH** Chemotherapy and RT →

∴ Excess **Combined** Risk of Second Cancer + Cardiovascular Disease.

Radiation for Stage II Seminoma

Author	Stage	N	Relapse
Mason (1988)	IIA/B	25	1 (4%)
	IIC	24	6 (25%)
Warde (1998)	IIA	40	4 (10%)
	IIB	24	3 (13%)
	IIC	14	7 (50%)
Patterson (2001)	IIA	46	6 (13%)
	IIB	34	9 (26%)
Zagars (2001)	IIA	6	0 (0%)
	IIB	38	5 (13%)
	IIC	25	3 (12%)
Classen (2003)	IIA	66	2 (3%)
	IIB	21	2 (10%)
Chung (2004)	IIA	49	4 (8%)
	IIB	30	4 (13%)
	IIC	16	10 (63%)

Radiation is a Standard of Care for Stage IIA and small IIB (<3cm)

Large Stage IIB and Stage IIC Seminomas Require Chemotherapy

IGCCCG Risk Groups for Seminoma¹

Risk Group	Features	5-yr OS	5-yr DFS
Good	No organ metastases other than lung (- NPVM)	86%	82%
Intermediate	+ NPVM	72%	70%
10%			

NPVM = non-pulmonary visceral metastases

NOTE: Marker levels and primary site **DON'T** affect outcome

¹IGCCCG, JCO, 1997

IGCCCG Risk Category Standard of Care

Table 1. The International Germ-Cell Cancer Collaborative Group prognostic grouping for seminoma and non-seminomatous germ-cell tumours

Parameter	Good	Intermediate	Poor
Seminoma			
h-fetoprotein	Normal	Normal	
HCG	Any	Any	
Lactate dehydrogenase	Any	Any	
Primary	Any	Any	
Other	No non-lung secondary tumours	Non-lung visceral secondary tumours	
% patients	90%	10%	
5-year survival	86%	72%	
Non-seminomatous germ-cell tumour			
h-fetoprotein	<1000	1000-10 000	>10 000
HCG	<5000	5000-50 000	>50 000
Lactate dehydrogenase	<1.5xULN	1.5-10xULN	>10xULN
Primary	Testis/retroperitoneum	Testis/retroperitoneum	Mediastinal
Other	No non-lung secondary tumours	No non-lung secondary tumours	Non-lung secondary tumours
% patients	56%	28%	16%
5-year survival	92%	80%	48%

HCG, human chorionic gonadotropin

Good Risk

Visceral mets: pulmonary

BEP x 3 or EP x 4

Intermediate Risk

Visceral mets: non-pulmonary

BEP x 4

Conclusions

GCT is highly curable.

Goal: Minimize toxicity--maintain high cure rate. Must remember and explain late toxicity.

Chemotherapy important but has toxicity.

Teratoma always considered in NSGCT.

RPLND in NSGCT important - bilateral, nerve-sparing is best. Experience counts!

Careful patient selection at each stage.

CS 2A/B Seminoma: NCCN Guidelines

2. CHEMOTHERAPY

Clin Stage	Total	Rel	DOD	Author
2A	20	0	0	Garcia-del-Muro, JCO 2008.
2B	72	6**	1	Giannis, J Cancer Res Clin Oncol 2009.
2A+2B	6+67	0	0	Tandstad, JCO 2011

****= ALL RELAPSES RECEIVED ETOPOSIDE 400 mg/m² (360 proven inferior to 500)**

Systematic Review: (Giannatempo et al, Ann Oncol 2015)

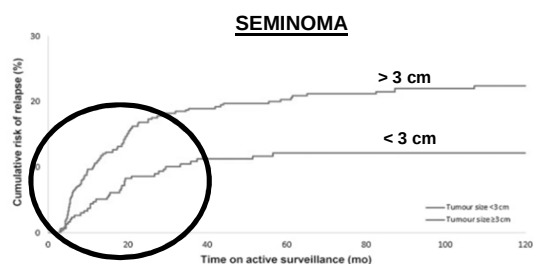
1. CS 2B relapse rate lower for Chemo than RT.
2. Second non-GCT cancer 4% in RT, 2% in CT.

Stage I GCT Active Surveillance Time to Relapse

	NSGCT LVI + n = 183	NSGCT LVI - n = 935	SEMINOMA n = 1,344
relapse	81 (44%)	132 (14%)	173 (13%)
<12 mo	73 (90%)	95 (72%)	73 (42%)
<24 mo	77 (95%)	118 (89%)	130 (75%)
<36 mo	79 (98%)	124 (93%)	160 (92%)
>36 mo	2 (2%)	8 (7%)	14 (8%)

Kollmannsberger et al; JCO 33:51; 2014

Surveillance for CS I GCT Princess Margaret Hospital



Nayan et al. Eur Urol; 2016

Radiation for Stage II Seminoma

Author	Stage	N	Relapse
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	IIB	30	4 (13%)
	IIC	16	10 (63%)

Radiation is a Standard of Care for Stage IIA and small IIB (<3cm)

Large Stage IIB and Stage IIC Seminomas Require Chemotherapy

CS I Seminoma: Carboplatin (Aparacio et al, JCO, 2011)

Risk Factors (unvalidated)

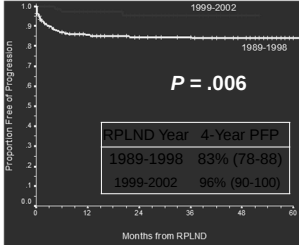
1. Tumor < 4 or > 4 cm
2. Rete Testis Invasion Present or Absent

Risk Factors	Treatment	%Relapse	Deaths
None	Surveillance	5%	0
<u>One Factor</u>			
>4cm	Surveillance	14%	0
Rete Testis		20%	
Both	Carbo x2	1.4%	0
TOTAL	----	7%	0

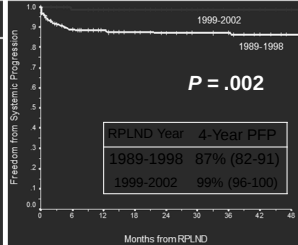
Median followup: 34 months

Changes in Clinical Outcome Over Time Stephenson AJ et al, JCO 2005; 23: 2781-8

MSKCC: Overall Disease Progression by Year*



MSKCC: Systemic Disease Progression by Year*



* Excluding patients receiving adjuvant chemotherapy



Predicting teratoma in RP Carver et al, JCO 2007

	<u>Hazard ratio</u>	<u>95% C.I.</u>	<u>P-value</u>
IGCCCG	0.61	0.35, 1.08	0.089
2 nd line chemo	0.51	0.26, 1.0	0.048
CT size pre-	0.77	0.7, 0.85	<0.005
CT size post-	1.6	1.4, 1.83	<0.005
ORCHIECTOMY			
teratoma	3.31	2.11, 5.21	<0.005
yolk sac	1.79	1.14, 2.83	0.012
embryonal ca	1.41	0.8, 2.5	0.2

Late Relapse of Testicular Cancer Definition

Most relapses in patients with low-stage and advanced GCT occur within 2 years of treatment

Relapse following a 2 year disease-free interval

Absence of second primary GCT

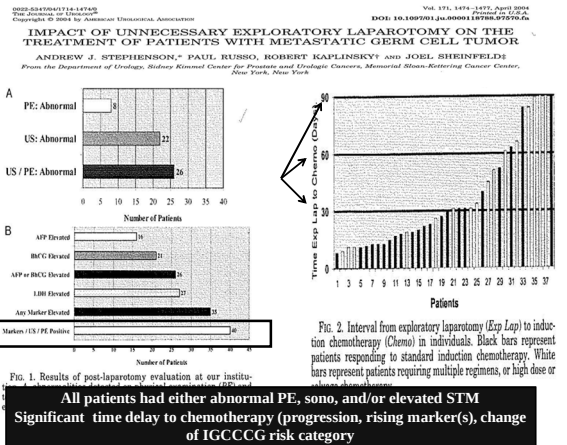
Incidence

~ 3% - 4% and appears to be increasing

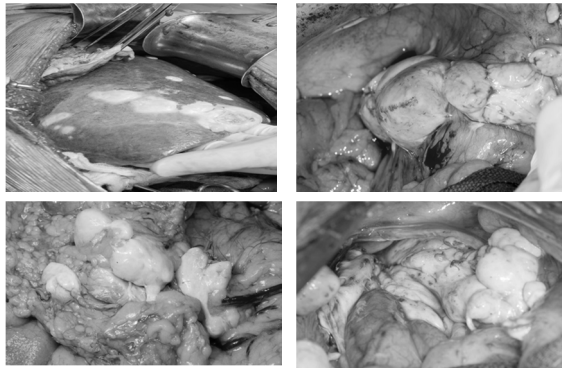
Oldenburg et al, JCO 2006; Oldenburg et al, Br J Cancer 2006

Late Relapse of Testicular Cancer Clinical Features

- Distinct clinical entity
- May occur at any time
- Chemoresistance
- Retroperitoneum is the most common site
- Decreased survival regardless of initial clinical stage



Carcinomatosis S/P lap RPLND (pN1)



Seminoma: Take home messages

Stage I

Survival 100%, relapse w/ size >4cm or rete testis +
Surveillance least toxic, need better risk factors

Stage II

IIA → XRT (10% relapse rate) or Chemo (0% relapse)
RPLND trial
IIB → small/solitary chemo or XRT
→ large/multifocal = chemo

Advanced Disease

EPx4 (MSKCC) or BEPx3 (Indiana) for good-risk
BEPx4 for intermediate-risk (NEVER POOR-RISK)
Post-chemo PET and size criteria for resection
More severe desmoplastic rxn post-chemo

Clinical Stage I and II NSGCT Management following 1° RPLND

Pathologic Stage	Criteria	Relapse rate (%)	Management
pN0	All nodes -	<10%	Observe
pN1	< 2cm <5 + nodes No ENE	10%-15%	Observe if compliant
pN2/3	>2cm >6+ nodes ENE present ??	>40%	Adjuvant CTX preferable (B)EP x 2**

**RPLND with therapeutic intent, post-op evaluation: NED

If rising STM, new pulmonary nodule -- INDUCTION CHEMOTHERAPY

Clinical Stage II NSGCT Summary

Importance of patient selection:

chemotherapy
all IIC, multifocal; >3cm and /or symptomatic IIB
any IIA/B/C with elevated and / or rising markers
RPLND
NORMAL markers
IIA, <3cm unifocal, asymptomatic IIB

Importance of optimal execution of selected treatment

RPLND with curative intent
Chemotherapy appropriate regimen according to IGCCCCG criteria

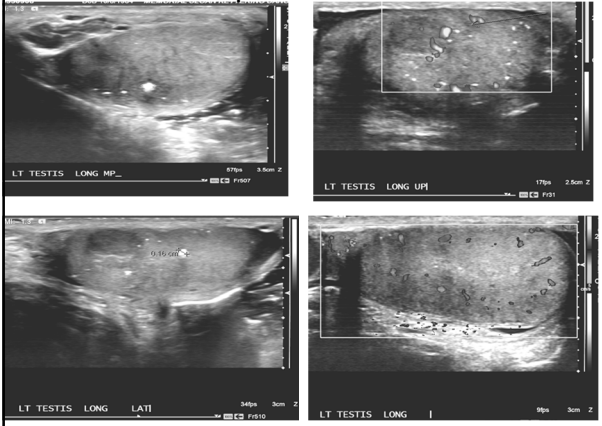
Subset of patients require dual therapy (optimal sequencing)

PC-RPLND all residual masses >1cm
adjuvant chemotherapy after primary RPLND: pN2/3, noncompliant pN1

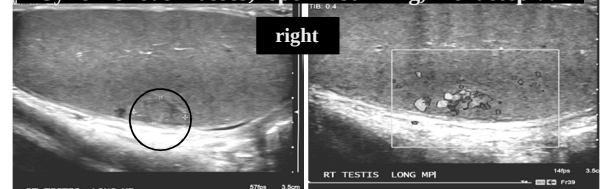
Adjuvant chemotherapy (B)EP x 2

post op patient MUST be NED;
if rising marker/ new nodule needs induction regimen

atrophic left testicle



Synchronous masses; sperm banking, next step ??



SPECIMEN:

A: Testis, left, orchiectomy B: Testis, right, mass, excision C: Tumor bed #1, biopsy D: Tumor bed #2, biopsy
E: Tumor bed #3, biopsy

DIAGNOSIS(ES):

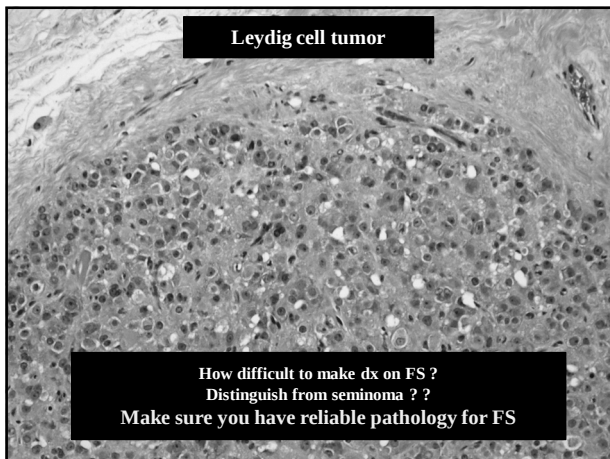
A. Testis, left, orchiectomy: Seminoma, classical type, 0.6 cm in largest dimension, not involving the tunica albuginea. No vascular invasion identified. No tumor seen in epididymis, spermatic cord and surgical margins. The remaining testis shows patchy atrophy and intratubular germ cell neoplasia.

B. Testis, right, mass, excision: Leydig cell tumor, histologically benign. The surrounding testis is unremarkable.

C. Testis, right, tumor bed #1, biopsy: Testis with normal spermatogenesis. No tumor or atypia seen.

D. Testis, right, tumor bed #2, biopsy: Testis with normal spermatogenesis. No tumor or atypia seen.

E. Testis, right, tumor bed #3, biopsy: Testis with normal spermatogenesis. No tumor or atypia seen.



Testicular Tumors: Clinical Evaluation

Required

History / Physical Exam

Scrotal U/S

(most RP primaries are testis in origin)

Serum AFP, BHCG, LDH

CXR

CT Chest, Abdomen, Pelvis

Only if clinically indicated

PET scan: (post - chemo seminoma)

no role in low-stage GCT, no better accuracy over CT
not capable of differentiating fibrosis from teratoma

MRI brain: pure chorio, neurologic symptoms

Serum Tumor Markers

IGCCCG Risk Group	Good S1	Intermediate S2	Poor S3
AFP	< 1000	1000-10,000	> 10,000
HCG	< 5000	5000-50,000	> 50,000
LDH	< 1.5x	1.5-10x	> 10x
Chemotherapy	BEPx3 EPx4	BEPx3	BEPx3

Chemotherapy regimen based on IGCCCG risk group
Marker status (S1-3) based on post-orchietomy nadir level

IGCCCG Risk Category Standard of Care

Table 1. The International Germ-Cell Cancer Collaborative Group prognostic grouping for seminoma and non-seminomatous germ-cell tumours

Parameter	Good	Intermediate	Poor
Seminoma			
α-fetoprotein	Normal	Normal	
HCG	Any	Any	
Lactate dehydrogenase	Any	Any	
Primary	Any	Any	
Other	No non-lung secondary tumours	Non-lung visceral secondary tumours	
% patients	90%	10%	
5-year survival	86%	72%	
Non-seminomatous germ-cell tumour			
α-fetoprotein	<1000	1000-10 000	>10 000
HCG	<5000	5000-50 000	>50 000
Lactate dehydrogenase	<1.5×ULN	1.5-10×ULN	>10×ULN
Primary	Testis/retroperitoneum	Testis/retroperitoneum	Mediastinal
Other	No non-lung secondary tumours	No non-lung secondary tumours	Non-lung secondary tumours
% patients	56%	28%	16%
5-year survival	92%	80%	48%

HCG, human chorionic gonadotropin.

Good Risk

Visceral mets: pulmonary

Marker levels: S1

EP x 4

BEP x 3

Intermediate/Poor Risk

Visceral mets: non-pulmonary

Marker levels: S2, S3

BEP x 4

Laparoscopic RPLND

Major Concerns

?? Therapeutic intent

?? Therapeutic efficacy (postop CTX >90%)

Unilateral templates >95% cases (regardless of findings)

Unusual patterns of metastases
Liver
Carcinomatosis
Port site

Steep learning curve

?? Inconsistencies in data

Advantages

Reduced postop morbidity
Shorter hospital stay
Less blood loss
Faster convalescence

No midline scar

Stage I NSGCT Active Surveillance Time to Relapse

	IA	IB
	NSGCT LVI - n = 935	NSGCT LVI + n = 183
relapse	132 (14%)	81 (44%)
<12 mo	95 (72%)	73 (90%)
<24 mo	118 (89%)	77 (95%)
<36 mo	124 (93%)	79 (98%)
>36 mo	8 (7%)	2 (2%)

Kollmannsberger et al; JCO 33:51; 2014

Stage I NSGCT Active Surveillance
Initial Detection of Relapses

	IA	IB
	NSGCT LVI -	NSGCT LVI +
	n = 935	n = 183
relapses	132 (14%)	81(44%)
Method 1 st detection		
Abd CT	63 (48%)	31 (38%)
markers	54 (41%)	49 (61%)
N/A	12 (9%)	

Kollmannsberger et al; JCO 33:51; 2014

Stage I GCT Active Surveillance
IGCCCG Risk of Relapses

	NSGCT LVI +	NSGCT LVI -
	n = 183	n = 935
relapses	81	132
IGCCCG risk		
Good	76 (94%)	116 (88%)
Int	3 (4%)	13 (10%)
Poor	2 (2%)	3 (2%)
STATUS		
NED	79 (98%)	126 (95%)
DOD	--	3 (2%)
Rx death	--	2 (2%)

Kollmannsberger et al; JCO 33:51; 2014

RPLND

- Once the decision is made to perform an RPLND, the surgeon should strive to maximize both the staging and therapeutic potential of the procedure. Bilateral templates accomplish this.
- Restricted templates unnecessarily increase probability of unresected RP metastasis; and despite effective cisplatin-based chemotherapy, the potential consequences include:
 - relapse, late relapse, re-operative RP surgery
 - increased burden of treatment
 - inferior clinical outcome in subset of patients
- Nerve-sparing techniques obviate the need for reduced templates

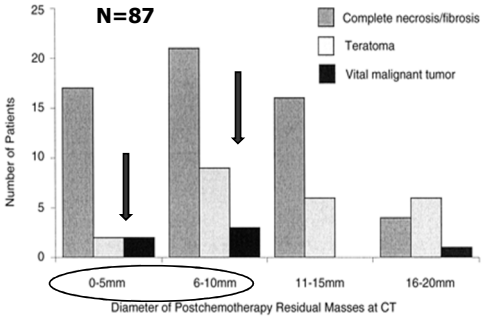
Stage I GCT Active Surveillance
Initial Detection of Relapses

	NSGCT LVI +	NSGCT LVI -	SEMINOMA
	n = 183	n = 935	n = 1,344
relapses	81 (44%)	132 (14%)	173 (13%)
Method 1 st detection			
Abd CT	31 (38%)	63 (48%)	150 (87%)
markers	49 (61%)	54 (41%)	6 (3%)
N/A		12 (9%)	17 (10%)

Kollmannsberger et al; JCO 33:51; 2014

Postchemotherapy Retroperitoneal Surgery Remains Necessary
In Patients With Nonseminomatous Testicular Cancer and
Minimal Residual Tumor Masses

By Jan Oldenburg, G. Cecilie Aflsen, Hans H. Lien, Nina Aass, Håkon Waehre, and Sophie D. Fosså





PENILE CANCER Update 2018

Curtis A. Pettaway, M.D.
Professor of Urology
The University of Texas
M. D. Anderson Cancer Center

Disclosure Statement

Advisory Role: Wolters Kluwer Publishing

PENILE CANCER Update 2018

- Incidence, Risk Factors, Prevention
- Management of the Primary Tumor
 - Organ Preserving Strategies
- Management of the Inguinal Region
 - Clinical Node Negative
 - Minimally invasive staging
 - Clinically Positive nodes
 - Assessment
 - Adjuvant/Neoadjuvant therapy
 - *InPACT Trial!*

Penile Carcinoma Demographics

Incidence ^(1,2)

- <1 case per 100,000 US males
- 26,300 cases worldwide
- 2-4 fold higher incidence
 - ♦ Cuba
 - ♦ Brazil
 - ♦ Columbia
 - ♦ Paraguay
 - ♦ India
 - ♦ Thailand

Age @ Diagnosis ⁽³⁾

- 55% ≤ 60
- 30% ≤ 50

(1) Parkin et al.: Cancer incidence in 5 continents Volume V: 1992
(2) Parkin et al.: Vaccine 24(Suppl 3):s3711-25, 2006
(3) Narayana et al.: Cancer 46: 1982

PENILE CARCINOMA Risk Factors

Prior to Puberty

- Lack of neonatal circumcision
- Poor hygiene
- Phimosis

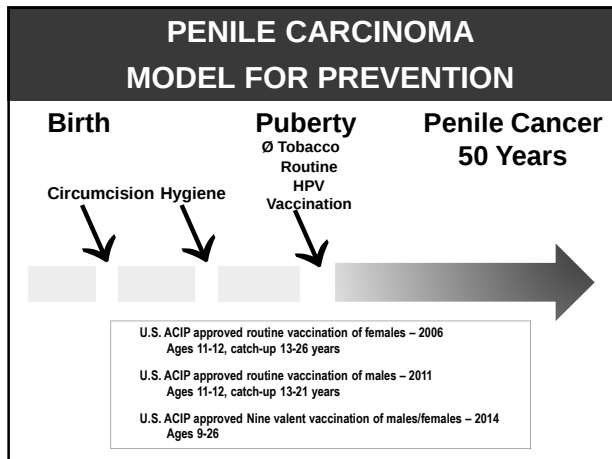
Maden et al.: J. Natl. Cancer Inst., 85:1993
Reddy et al.: Urology, 24: 1984

PENILE CARCINOMA Risk Factors

After Puberty

- Number of Sexual Partners
- HPV Infection
 - viral warts 6,11
 - Cancer 16,18,31,33,45,52,58
- Tobacco Products
 - Cigarette Smoke
 - Chewing Tobacco
 - Areca Nut (Snuff)
- Inflammation
 - Trauma, rash
 - Lichen Sclerosis

Maden et al.: J. Natl. Cancer Inst., 85:1993
Weiner et al.: Surg. Oncol. Clin N. Am., 4: 1995
Harish et al.: Brit. J. Urol., 73: 1995
Micall et al.: Sex Trans Infect 77:2001
Eisenle et al Arch Dermatol 144: 591, 2008



Carcinoma of Penis: Diagnosis

- Location**
 - Glans - 48%
 - Prepuce (foreskin) - 21%
 - Glans & prepuce - 9%
 - Coronal sulcus - 6%
 - Shaft <2%
- Implication**
 - Amenable to early diagnosis and treatment
 - Delayed presentation common!

Sufrin and Huban 1991

Netter Images

PENILE CARCINOMA Evaluation

- History**
- Physical Examination**
 - Penis
 - Inguinal Lymph Nodes
- Imaging**
 - Penis- MRI
 - Inguinal lymph nodes- MRI, CT scan, Ultrasound guided FNA, PET/CT scan
- Lesion Biopsy**
 - Establishes diagnosis, grade, and pT stage
 - Excisional
 - Incisional
 - Punch Biopsy

TMN Staging American Joint Committee (AJCC) on Cancer Staging for Penile Cancer: Eighth Edition

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Penile intraepithelial neoplasia [PeIN])
Ta	Noninvasive localized squamous cell carcinoma

T Category	T Criteria
T1	Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade
T1a	Tumor is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid)
T1b	Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)
T2	Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
T3	Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion
T4	Tumor invades into adjacent structures (i.e., scrotum, prostate, pubic bone)

Fig. 3. T2a, T2b and T3 tumor survival curves

pT-category detail

- T2a (n=155)
- T2b (n=175)
- T3 (n=24)

Pettaway et al. Penile. In AJCC Cancer Staging Manual 8th Springer 2017
Leijte et al. J Urol 180: 933, 2008

Penile Cancer: Stage T2 MRI

Figure 4. Ulcerating lesion on the glans (white arrowheads, with a white arrow showing the ulcerated part). pT2 on histology and correctly called T2 on MRI. CC, corpus cavernosum; S, the spongiosum part of the glans.

Kirkham. Br J Radiol 85(1):S86-93

Penile Cancer: Stage T3 MRI

Sagittal T2-weighted image shows large hypointense tumor mass replacing glans and extending to the shaft infiltrating corpora cavernosa

Kochhar et al. Eur Radiol 20:36, 2010

Penile Cancer Natural History*

- Primary lesion
- Dissemination
 - Lymphatic +++
 - Hematogenous +/-
- Metastases (lungs, liver, bone, brain)
- Death → regional complications



Courtesy: ACL Pompeo

Penile Carcinoma Traditional Amputation

- Provides excellent local control
 - Recurrence 0-8%
- Necessary in bulky Stage T2-T4
- Stratifies patient risk for Lymph node metastasis



Pettaway CA et al: Tumors of the penis. In: Campbell-Walsh Urology, 9th ed. WB Saunders 2007; p 959.
Djaladinirad et al J Urol 192: 120, 2013

Penile Amputation: The Problem

- Young age @ Diagnosis⁽¹⁾
 - Median = 62 years
 - 43% < 60
 - 30% < 50
- Traditional Amputation Decreases Sexual Quality of Life⁽²⁾
 - ↓ Erectile Function 8/18 (44%)
 - ↓ Desire 6/18 (33%)
 - ↓ Frequency 12/18 (66%)
 - ↓ Satisfaction 10/18 (55%)
- Regret⁽³⁾
 - 30% would choose penile preservation over longer survival
- Psychological well being/stress
 - Impaired in up to 40% of patients
 - Depressive symptoms in up to 31% of patients

(1) Hegarty et al. BJU Int. 98:526, 2006.
(2) Romero et al. Urology 66:1282, 2005.
(3) Ojijdsma et al. Brit J Urol 73:554, 1994
(4) Maddineni et al. BMC Urology 9:8, 2009.

Penile Cancer Organ Preservation Strategies

Goals

- Effective Local Control
- Organ Functionality
- Cosmetic Appearance



Penile Preservation: Observations⁽¹⁾

- Agrawal performed partial or total amputations
 - Measured microscopic extent from gross margin
 - Grade I-II, only 13% extended to 5mm
 - Grade III, 41% to 5mm, 25% extended to 10mm
 - “2 cm tumor free” margin not supported!

(1) Agrawal et al., Brit J Urol 85:299, 2000 – 64 patients, Clinical Stage ≥ T2
No skip lesions noted. Recommend: 10 mm margin Grades 1-2, 15 mm margin Grade 3

Penile Carcinoma Organ Preservation Strategies: Selection

- Optimal Tumors
 - Tis, Ta, T1 Grade 1-2
 - Easier to obtain local control
 - Metastatic rates 0 - 10%
 - Procedures
 - Glans resurfacing
 - Laser ablation
 - Excisions/reconstruction
- Select Tumors
 - Distal T2, Low grade
 - Procedures
 - Glans sparing excisions
 - Glansectomy with reconstruction



Penile Carcinoma In Situ Treatment Options

- **Surgical Excision**
 - 5 mm margin, underlying tissue
 - Glans resurfacing
- **Laser**
 - CO₂, Neodymium:YAG, KTP
- **Moh's Excision**
 - Pathologic expertise, facilities
- **Topical therapy**
 - 5 Fluorouracil
 - Imiquimod



Gerber, J. Urol., 151:1994
Goette et al., Cancer, 38:1976
Brown et al., J. Dermatol. Surg. Oncol
Alnajjar et al. Eur Urol 2012
Shabbir et al Eur Urol. 2011

Carcinoma In Situ Glans Penis Topical Therapy

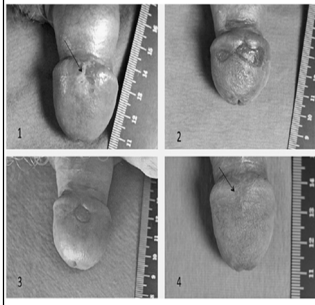


Table 3 - Overall response rates, local toxicity, and adverse events after 5-fluorouracil or imiquimod treatment

Treatment	CR	PR	NR	Local toxicity	Adverse events
5-FU, no.	21	13*	13	4	5
5-FU, %	50	31	31	10	12
IQ, no.	4*	0	5	0	1
IQ, %	44	0	56	0	11

CR = complete responders; PR = partial responders; NR = nonresponders;
5-FU = 5-fluorouracil; IQ = imiquimod.
*Seven PR developed subsequent complete response (five following subsequent 5-FU and two following subsequent IQ treatments).
**Two patients received second-line IQ because they had previously failed 5-FU treatments at other centres before referral.

Alnajjar, et. al. European Urology 2012. 44 eligible patients treated with 5-fluorouracil or imiquimod. Mean FU=34mos

Penile Carcinoma In Situ Laser Therapy

Series	Treated Area		No. Patients	Local Recurrence Number (%)	Mean Follow-ups (mos)
	Cancer	Premalignant			
Van Bezooijen ⁽¹⁾	Yes	No	19	5 (26)	25
Meijer ⁽²⁾	Yes	No	6	4 (67)	38
Teitjen ⁽³⁾	Yes	Yes*	12	1 (8)	58
Frimberger ⁽⁴⁾	Yes	Yes*	17	1 (6)	47

*5% Acetic Acid used to treat additional areas.
⁽¹⁾ J Urol 166:1670, 2001; Neodymium: YAG or CO₂ Laser, mean follow-up = 25 mos.
⁽²⁾ Urology 69:759, 2007; Neodymium: YAG Laser, mean follow-up = 38 mos.
⁽³⁾ Urology 52:559, 1998; CO₂, KTP, Neodymium: YAG, mean follow-up = 58 mos.
⁽⁴⁾ J Urol 168:2418, 2002; Neodymium: YAG Laser, mean follow-up = 47 mos.

Penile Carcinoma In Situ Laser Therapy



Penile Squamous Carcinoma in Situ Glans Resurfacing: University College Experience 2001-2010

- **Patients**
 - Total Glans Resurfacing (TGR)
 - N=10
 - Partial Glans Resurfacing (PGR)
 - N=15
- **Follow-up**
 - Every 3 mos. x 2 yrs.
 - Every 6 mos. x 2 yrs.
 - Mean = 29 mos. (2-120)
- **Graft Take**
 - 24/25 (96%)
- **No Post-Op Complications**

No. of cases	Positive	Further	Reoperation	Reoperation	Involved	Recurred	Progress	PGR = partial glans resurfacing	TGR = total glans resurfacing
25	12 (48)	7 (28)	2 (8)	5 (20)	1 (4)	0 (0)	0 (0)	15	10
									gin: TGR =

Shabbir et al. Eur Urol 59:142, 2011
Hegarty, et al. World Journal of Urology, 2008

Traditional Amputation: Glans Penis Tumor



Courtesy: Von Poppel

Glans Penis Tumor Glansectomy



Penile Cancer Organ-Sparing Surgery

Series	No. Patients	Procedures	Margin Status		Distance To Margin (%)	Incidence Recurrence (%)	Follow-Up (Months)
			Neg	Pos			
Minhas et al. ⁽¹⁾ UK	51	Wide Excision Glansectomy	51	-	0-10mm (48) 0-20mm (90)	2 (4) 2 (6) (3)	26 medium
Smith et al. ⁽²⁾ UK	72	Wide Excision Glansectomy	55	6	0-5mm (61) 26mm (39)	3 (4)	27 mean
Morelli et al. ⁽³⁾ Italy	17	Wide Excision Glansectomy	15	-	NS	0	36 mean
Kane et al. ⁽⁴⁾ Ireland	19	Wide Excision Glansectomy	NS	NS	NS	1 (5)	26 mean
Li et al. ⁽⁵⁾ China	32	Wide Excision Extended Circumcision	32	-	NS	3 (9)	26.5 median
Feldman et al. ⁽⁶⁾ USA	56	Excision, partial glansectomy, topical	42	14	NS	12 (21)	5 years median
Philippou et al. ⁽⁷⁾ UK	179	CIRC, WLE glansectomy, distal corporectomy	167	12	5mm (mean)	16 (8.9)	43 mean

(1) BJU Int 96:1040, 2005

(2) Eur Urol 56:1779, 2007

(3) Int J Impot Res 21:311, 2009

(4) Advances Urol doi:10.1155/2011/240824

(5) Urology 28:1121, 2011

(6) J Urol 186:1303, 2011

(7) J Urol 188:363, 2012

Penile Cancer Organ Sparing Surgery Local Relapse

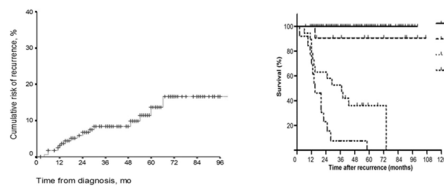


Figure 1. Cumulative risk of local recurrence (Kaplan-Meier method, 1 - survival).

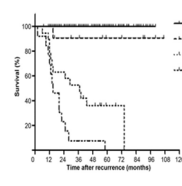


Figure 2. Disease specific survival after local, regional and distant recurrence.

Predictors
Grade 3, $p = 0.003$
Stage $\geq T2$, $p = 0.021$
LVI, $p = 0.014$
Margin Distance = NS

Philippou et al., J Urol 188:803, 2012

Penile Cancer Organ-Sparing Surgery/Radiotherapy Complications

Series	No. Patients	Procedures	No. Complications(%)	Type Complication
Smith et al. ⁽¹⁾	72	Wide Excision Glansectomy	3(4)	Partial graft loss Urethral stenosis
Morelli et al. ⁽²⁾	15	Wide Excision Glansectomy	4(27)	Partial graft loss Urethral stenosis Phimosis
Kane et al. ⁽³⁾	19	Wide Excision Glansectomy	2(10.5)	Urethral stenosis
Crook et al. ⁽⁴⁾	67	Ir wires Seeds, PDR	(21)	Necrosis Urethral stenosis
De Crevoisier ⁽⁵⁾	144	Ir wires	(45)	Ulceration/necrosis Urethral stenosis

(1) Eur Urol 52:1179, 2007

(2) J Impot Res 21:311, 2009

(3) Advances Urol doi:10.1155/2011/240824

(4) World J Urol: 27:189, 2009

(5) Int J Radiation Oncology Biol Phys 74(4):1150-56, 2009

Penile Carcinoma Organ Preserving Strategies

- Feasible in Stage Ta, T1, Tis – T1, Small T2
- Sexual QOL
 - Favorable Laser, limited excisions
 - Additional studies required
- Complication rates
 - Surgery – low
 - Radiation – low – moderate
- Higher incidence local recurrence
 - Survival was not adversely impacted
 - Achieving negative margins important
 - Careful long-term follow-up required!
 - Early biopsy for suspicious lesions.

Penile Cancer Requirements for Surgical Cure⁽¹⁻¹⁰⁾

- Limited unilateral inguinal metastases
1-2 unilateral nodes, > 70% 5 year disease free survival
- ≥ 3 unilateral or bilateral metastases
12 – 60% 5 year disease free survival
- Extranodal cancer extension
5 – 6% 5 year disease free survival
- Pelvic lymph node metastases
10% 5 year survival

⁽¹⁾ Horenblas et al., J Urol 149:1393

⁽²⁾ Smith et al., J Urol 137:1387

⁽³⁾ Sun et al. BJUJ 2014

⁽⁴⁾ Ravi. Br J Urol 72:1993

⁽⁵⁾ Johnson et al., Urol 24:1984

⁽⁶⁾ Li et al. Br. J Cancer 2015

⁽⁷⁾ deKernion et al., Cancer 32:1973

⁽⁸⁾ Powesing et al., Semin Surg Oncol 6:1990

⁽⁹⁾ Kamal et al., J Surg Oncol 52:1993

⁽¹⁰⁾ Reddy et al. BJUJ Int PMS25

Penile Cancer Inguinal Lymph Node Dissection (ILND)/Staging Procedure

Indicated:

- Patients with palpable inguinal adenopathy

Advised:

- Patients with no palpable lymph nodes
 - *NCCN, EAU guidelines favor early Staging/ILND among select patients*

Hakenberg et al Eur Urol 67:142, 2015
NCCN Clinical Practice Guidelines 2016

Penile Cancer: Primary Tumor Pathologic Stage & Inguinal Lymph Node Metastases: TNM 8th Edition

T Category	T Criteria	Stage	pN+	Risk
T1	Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade	≤ T1a	0-18%	Low
T1a	Tumor is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid)	T1b	33-50%	High
T1b	Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)	T2	33-35%	High
T2	Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion	T3-T4	49-53%	High
T3	Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion	Inguinal Management ≤T1a- Observation, inguinal staging if noncompliant ≥T1b- Inguinal staging recommended		
T4	Tumor invades into adjacent structures (i.e., scrotum, prostate, pubic bone)			

Pettaway et al. AJCC Staging Manual 8th ED Springer 2017
Sun et al BJU Int; 116 734, 2014

PENILE CANCER STAGING STRATEGIES TO MINIMIZE MORBIDITY

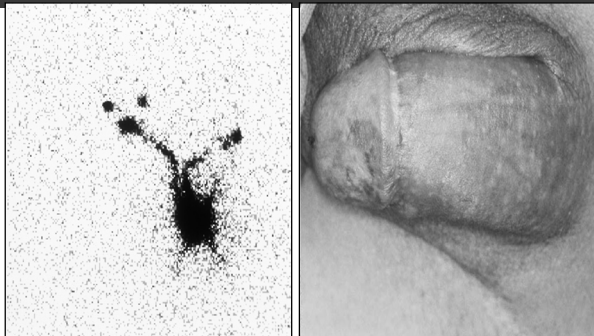
- Sentinel or extended lymph node biopsy (SLNB)^(1,2)
- Dynamic Sentinel node Biopsy⁽³⁾
- Superficial/modified dissections^(4,5)
- Lap/Robotic Lymphadenectomy⁽⁶⁻⁷⁾

¹ Cabanas: Cancer, 39:1977
² Pettaway: J Urol, 154:1995
³ Horenblas: J Urol; 163: 2000
⁴ Catalona: J Urol, 140, 1988
⁵ Spiess: J Urol, 177, 2007
⁶ Tobias-Machado: J Endo Urol 22, 2008
⁷ Martin et al : BJUI 2013

Dynamic Sentinel Lymph Node Biopsy Goal

To determine where in the inguinal lymph node field the “sentinel” node resides in the individual patient.

Dynamic Sentinel Node Biopsy

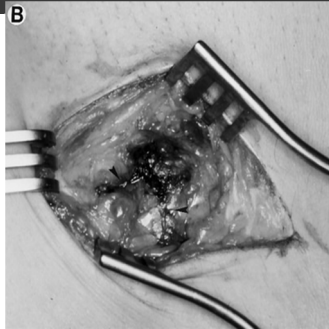


Dynamic Sentinel Node Procedure



Horenblas et al. J Urol 163: 102, 2000

Dynamic Sentinel Node Procedure



Horenblas et al., J Urol 163:102, 2000

Dynamic Sentinel Lymph Node Biopsy (DSNB): Modified Technique⁽¹⁾ Results From High Volume Centers

Series	No. Patients	No. Groins Metastases	DSNB Detected Metastases Number (%)	Follow-up (mos) Median
Leijte, et al. ⁽²⁾	58	21	20/21 (95)	30
Hadway, et al. ⁽³⁾	75	22	21/22 (95)	11
Leijte, et al. ⁽⁴⁾	323	85	79/85 (93)*	18
Kirrandar et al. ⁽⁵⁾	57	13	11/13 (85)*	21

(1) Ultrasound with needle inspiration before DSNB; Exploration of nonvisualized groins; serial sectioning of sentinel node with immunohistochemistry.

(2) Eur Urol 52:170, 2007 BJU Int 100:561, 2007

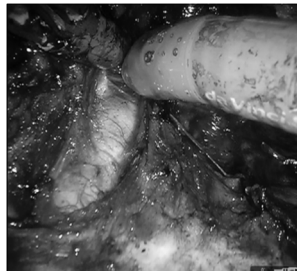
(3) BJU Int 100:561, 2007

(4) J Clin Oncol 27(20):3325, 2009. *On follow-up 4/6 patients with false negative DSNB died of disease

(5) BJU Int 111:48-53 2013. *On follow-up 2 patients with false negative DSNB died of disease

Penile Carcinoma Superficial Inguinal Lymph Node Dissection⁽¹⁻⁴⁾

- Removes nodal tissue above fascia lata
- Frozen section
- Limited morbidity
- Identifies "First Echelon" lymph nodes
- Saves Saphenous Vein
- Rare inguinal recurrences!



(1) Bevan-Thomas et al., J. Urol., 157:1638, 2002

(2) Pompeo et al., J. Urol., 153: 246A, 1995

(3) Puras - Baetz et al., J. Urol., 153:246A, 1995

(4) Spiess et al J Urol 177:2157, 2007. No recurrences among 23 patients with a negative superficial inguinal dissection at 3 years

(5) Martin et al : BJUJ 2013

Complications of DSNB, Laparoscopic Modified / Superficial Inguinal Lymphadenectomy

Study	Surgical Approach	#Complications/ #Groins	†Complication Rate (%)
Kroon, et al. ⁽¹⁾	DSNB	14/189	7
Tobias-Machado, et al. ⁽²⁾	Laparoscopic	2/10	20
Sotelo, et al. ⁽³⁾	Laparoscopic	3/14	21
Bouchot, et al. ⁽⁴⁾	Modified	12/118	12
Bevan-Thomas, et al. ⁽⁵⁾	Superficial	23/66	35
Spiess, et al. ⁽⁶⁾	Superficial	15/52*	29

DSNB=dynamic sentinel node biopsy. Modified=modified inguinal lymph node dissection template. Superficial refers to nodes removed above the fascia lata of the thigh. Laparoscopic refers to a minimally invasive percutaneous approach to removal of inguinal nodes. Please see references for specific surgical techniques.

†Complication percent rounded to the nearest whole number

*Among 26 patients undergoing superficial dissection with negative lymph nodes

(1) J Urol 173:813, 2005

(2) J Urol 177:953, 2007

(3) J End Urol 21:364, 2007

(4) Eur Urol 45:761, 2004

(5) J Urol 167:1638, 2002

(6) World J Urol; 27:205, 2009

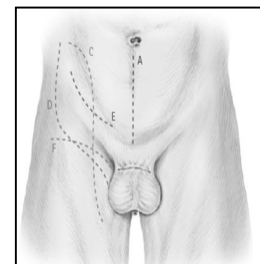
Inguinal STAGING: No Palpable Adenopathy- Contemporary Strategies

- Dynamic Sentinel Node Biopsy
 - NCCN, EAU guidelines
- Superficial/modified dissections
 - NCCN, EAU guidelines
- Lap/Robotic Lymphadenectomy
 - Option at experienced centers

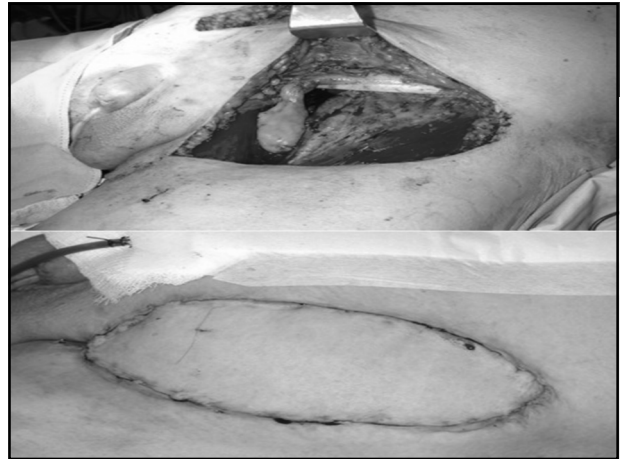
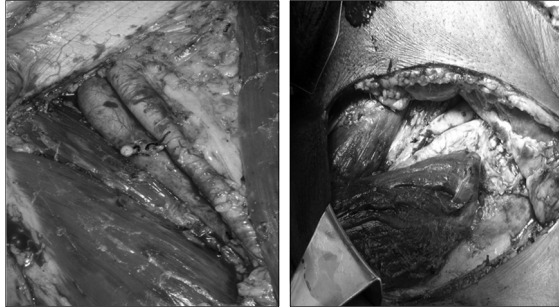
Spiess et al. J Natl Comp Canc Net 11:659, 2013; Pizzocaro et al. 57:1002, 2010; Horenblas: J Urol:163:2000; Catalona: J Urol, 140, 1988; Spiess: J Urol, 177, 2007; Tobias-Machado: J Endo Urol 22, 2008; Master J Urol 188: 1176, 2012; Schwentner et al J Endourol 27:497, 2013; Martin et al : BJUJ 2013

Penile Carcinoma: Traditional Inguinal/ Ilioinguinal Lymphadenectomy

- Proven Metastasis
 - Efficacy justifies morbidity
- Goals
 - Eradicate all cancer
 - Adjuvant therapy candidate
 - Technical
 - Cover exposed vasculature
 - Provide for rapid wound healing



Traditional ILND: Sartorius Muscle Transposition



PENILE CANCER Palpable versus No Palpable Adenopathy: Pathologic Features

Table 2. cN status and inguinal dissected specimen histopathological parameters

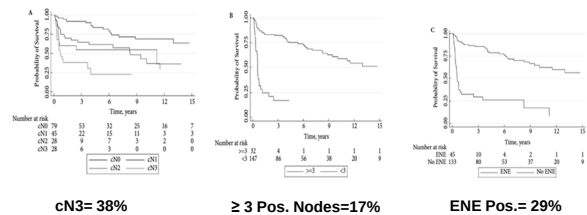
	No. cN0 (%)	No. cN+ (%)	p Value
Overall	45	111	
No. unilateral metastatic inguinal lymph nodes:			0.005
2 or Less	40 (89)	71 (64)	
3 or Greater	5 (11)	36 (32)	
Metastatic mass*	—	4 (4)	
Metastatic inguinal lymph node ENE:			<0.001
No	39 (87)	38 (34)	
Yes	6 (13)	73 (66)	
Dissected inguinal specimen surgical margin:			0.2
Neg	45 (100)	104 (94)	
Pos	0	7 (6)	
Pelvic lymph node involvement:			<0.001
No	44 (98)	78 (70)	
Yes	1 (2)	33 (30)	
Postop radiotherapy:			<0.001
No	37 (82)	49 (44)	
Yes	8 (18)	62 (56)	

Graafland et al. J Urol 184: 1347, 2010: 156 chemotherapy naïve node positive patients treated with primary ILND

Factors associated with regional recurrence after lymph node dissection for penile squamous cell carcinoma

Jay P. Reddy*, Curtis A. Pettaway¹, Lawrence B. Levy*, Lance C. Pagliaro², Pheroze Tamboli³, Priya Rao³, Isuru Jayaratna⁴ and Karen E. Hoffman*

Three Year Relapse Free Survival



BJU Int 119: 591, 2017- 182 patients treated with Inguinal/pelvic lymphadenectomy
Multivariate predictors of relapse free survival-Clinical N3 stage, ≥3 positive inguinal lymph nodes, extranodal extension (ENE)
Neoadjuvant chemotherapy-27.5% Adjuvant Chemotherapy-7.7% Adjuvant Radiotherapy 5%

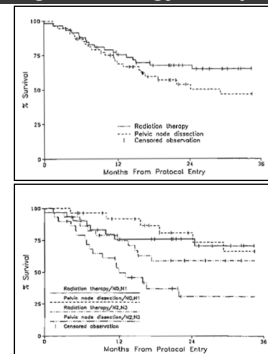
PENILE CANCER Adjuvant Strategies Post Lymphadenectomy

- Radiation
- Chemotherapy

How should these strategies be integrated to improve survival?

VULVAR CANCER Ilioinguinal Versus Inguinal Dissection and XRT Randomized Trial: Gynecologic Oncology Group

- Randomized Patients
 - 59 Inguinal Dissection and XRT
 - 54, Inguinal and Pelvic Dissection
- Treatment Groups
 - Prognostic Factor Equal
- XRT
 - Bilateral Groins and Pelvis
 - 4500-5000 RAD
- Groin Recurrence
 - XRT = 5.1%
 - Surgery = 23.6%
- Pelvic/Local Recurrence
 - No difference



Homesley et al. Obstet Gynecol 68:733, 1986

Original article

Adjuvant chemotherapy is associated with improved overall survival in pelvic node-positive penile cancer after lymph node dissection: A multi-institutional study

Pranav Sharma, M.D.¹, Rosa Djajadiningrat, M.D.², Kamran Zargar-Shoshtari, M.D.³, Mario Catanzaro, M.D.⁴, Yao Zhu, M.D.⁵, Nicola Nicolai, M.D.⁶, Simon Horenblas, M.D., Ph.D.⁷, Philippe E. Spiess, M.D.⁸⁻¹⁰

N= 85 patients, pN3

- Four Centers

Cisplatin, VBM Adjuvant Chemo

- Yes, N= 36
- No, N= 48

No chemotherapy cohort

- Older
- Higher pTstage
- ↑ Adjuvant XRT
- ↓ ENE, inguinal, pelvic nodes

Adjuvant Chemo

- 11 mos ↑ survival
- > 21 versus 10
- Independent predictor of survival

Follow-up (months)	0	10	20	30	40	50	60
No ad. chemo (n=48)	48	36	26	18	17	16	15
Yes ad. chemo (n=36)	36	31	21	19	15	14	13

Fig. OS of AC vs. no AC in chemotherapy-naïve patients with pN3 who have PPLN.

Urol Oncol 33: 17, 2015

Penile Cancer Guidelines: Adjuvant Therapy High Risk Post Inguinal Lymphadenectomy

NCCN¹

- pN2-3
- Radiation, Chemo-radiation or Chemotherapy

EAU²

- pN2-N3
- Chemotherapy

¹ NCCN Clinical Practice Guidelines 2016

² Hakenberg et al. Eur Urol 67: 2015

Neoadjuvant Therapy: Patient Selection

Sometimes its Obvious!

Neoadjuvant Therapy: Patient Selection

Sometimes its Not so Obvious!

Identification of High Risk Pathological Node Positive Penile Carcinoma: Value of Preoperative Computerized Tomography Imaging

Niels M. Graafland, Hendrik J. Teertstra, A. Peter E. Besnard, Hester H. van Boven and Simon Horenblas*

From the Departments of Urology (NMG, SH), Radiology (HJT, APEB) and Pathology (HHVB), The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Table 3. Evaluation of radiographic criteria in the prediction of histopathological high risk pN+ penile cancer

	No. High Risk pN+ Features*		Sensitivity	Specificity	Accuracy	PPV	NPV
	No	Yes					
Short-axis diameter 8 mm or greater:							
No	22	1	21/22 (95)	22/38 (58)	43/60 (72)	21/37 (57)	22/23 (96)
Yes	16	21					
Short-axis diameter 11 mm or greater:							
No	24	2	20/22 (91)	24/38 (63)	44/60 (73)	20/34 (59)	24/25 (92)
Yes	14	20					
Short-axis diameter 15 mm or greater:							
No	32	4	18/22 (81)	32/38 (84)	50/60 (83)	18/24 (75)	32/36 (89)
Yes	6	18					
Central nodal necrosis:							
No	31	3	19/22 (86)	31/38 (82)	50/60 (83)	19/26 (73)	31/34 (91)
Yes	7	19					
Presence of irregular nodal border:							
No	36	5	17/22 (77)	36/38 (95)	53/60 (88)	17/19 (89)	36/41 (88)
Yes	21	17					
Infiltration of adjacent tissue:							
No	37	7	15/22 (68)	37/38 (97)	52/60 (87)	15/16 (94)	37/44 (84)
Yes	11	10					
Central nodal necrosis or irregular nodal border:							
No	31	1	21/22 (95)	31/38 (82)	52/60 (87)	21/28 (75)	31/32 (97)
Yes	21	21					

* Only those groups with histopathologically proven 3 or more metastatic inguinal nodes and/or ENE and/or pelvic nodal involvement were considered high risk.

† These groups had inguinal lymph node metastases but were classified low-risk (that is 2 or less inguinal metastatic nodes without ENE).

Inter Observer Agreement 92-93%

J Urol 185-881, 2011

Preoperative Identification of High Risk Lymph Node Metastasis CT Scan Criteria*

A: Axial CT scan showing a large, enhancing mass in the right hemipelvis.

B: Axial CT scan showing a large, enhancing mass in the right hemipelvis.

C: Axial CT scan showing a large, enhancing mass in the right hemipelvis.

*Graafland et al. J Urol 185: 881, 2011, ≥ 3 positive nodes, extranodal extension, pelvic nodal metastasis

Chemotherapy for Advanced Penile Squamous Carcinoma

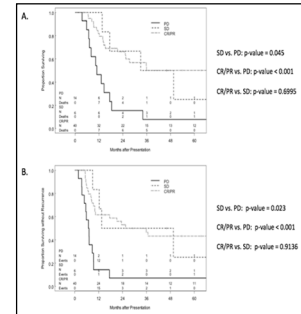
Series	Regimen	No. Pts.	Objective Response No. (%)	Median Survival Months
Nicholson ⁽¹⁾	T,P, F	26	10 (38.5)	7.7 (NS)
Djajadiningrat ⁽²⁾	T,P,F	26	11 (44)	10 (6.7-28.1)
Pagliari ⁽³⁾	T,I,P	30	15 (50)	17 (10-60+)

⁽¹⁾BJC 109: 2554, 2013- patient s with advanced regional or distant metastatic penile cancer treated with docetaxel, cisplatin, 5 Fluorouracil chemotherapy
⁽²⁾ Clin Genitourin Cancer 13:44, 2015 – advanced regional metastases
⁽³⁾ J Clin Oncol 28: 3851,2010- advanced regional metastases treated with paclitaxel, cisplatin ifosfamide chemotherapy

Overall Survival according to TIP Chemotherapy Response @ 5 years

Characteristic	Value
Demographics and clinical characteristics	
Number of patients	61
Median (range) age, years	60.6 (24.3-81.4)
Race, n (%)	
Caucasian	41 (67.2)
Hispanic	16 (26.2)
African American	4 (6.6)
Initial clinical stage, n (%)	
N1	2 (4.9)
N2	20 (32.8)
N3	37 (60.4)
N0	1 (1.6)
Chemotherapy response	
Number of patients	60
Chemotherapy response, n (%)	
TIP	53 (88.3)
Non-TIP	7 (11.7)
Clinical response to chemotherapy, n (%)	
Progression	14 (23.3)
Stable disease	8 (13.3)
Partial or complete response	38 (63.3)
Unknown	1 (1.7)
Outcomes after surgery	
Number of patients	52
Pathological stage, n (%)	
pN1	10 (19.2)
pN2	8 (15.4)
pN3	25 (48.1)
Overall outcomes	
Number of patients	61
Disease status at 5 years*, n (%)	
Alive without disease	20 (32.8)
Alive with disease	2 (4.9)
Dead from other noncancer causes	0 (0.0)
Dead from disease	32 (52.3)

*No measurable disease. Patients received one course of chemotherapy and was lost to follow-up due to non-compliance. Patient eventually died from disease. (Median range) follow-up among 50 patients without disease 67 (10-180) months.



Dickstein et al. BJU 117: 118, 2016- 61 patients with advanced regional metastases treated with preoperative Chemotherapy with curative intent- 65% of patients with CR/PR and 50% alive @ 5 years

International Penile Advanced Cancer Trial (InPACT) ECOG-EA8134



Steve Nicholson M.D., InPACT Study Chair
 Curtis Pettaway, M.D. InPACT Trial Study Chair, USA
 Dan Canter, M.D. ECOG Surgical Chair
 Juanita Crook, M.D., InPACT Study Chair, Canada

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
 Making Cancer History®



InPACT Trial: Important Questions

Question #1-InPACT Neoadjuvant

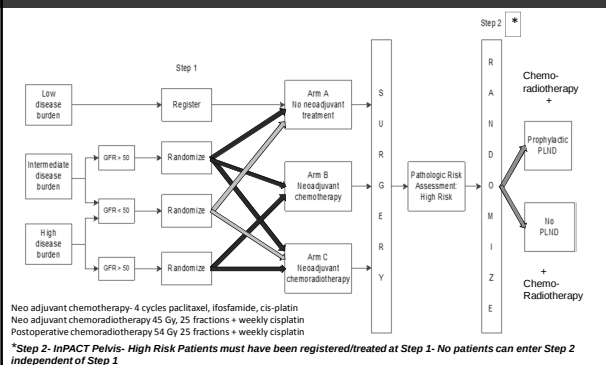
- What is the role of neoadjuvant therapy?
- Does either chemotherapy or chemoradiation provide superior outcomes?

Question #2- InPACT Pelvis

Among patients with prior ILND and adverse features receiving chemoradiation what is the role of prophylactic PLND?

- ≥ 3 positive nodes, extranodal extension
- Bilateral metastases

InPACT Trial: Positive Lymph Nodes



InPACT Trial: North American Accrual Goal

Target

- 200 patients USA, Canada
 - ECOG, SWOG, Alliance, NRG, NCIC
- 400 Total

Primary Endpoint

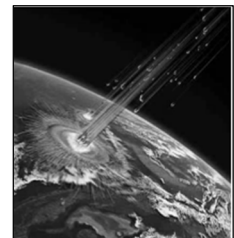
- Survival

Secondary endpoint

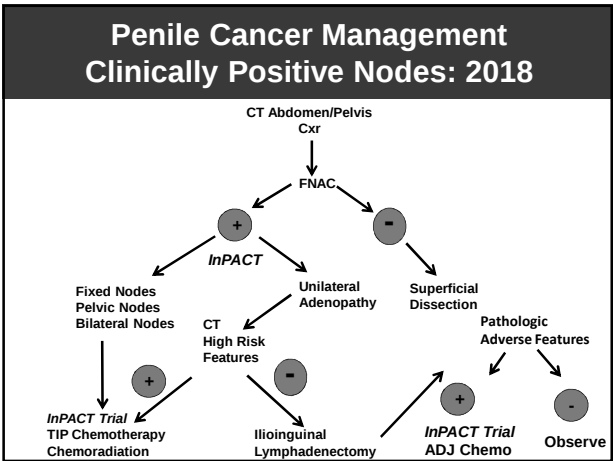
- DSS, DFS, DMFS, LRFS, pN0
- Toxicity
- Surgical complications
- QOL
- Feasibility of delivering treatment

InPACT Trial Information

➤ <http://ecog-acrin.org/clinical-trials/ea8134-educational-materials>



Open and Accruing!





Urethral Carcinoma: Update 2018

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Disclosure Statement

- Advisory Role: Wolters Kluwer Publishing

Urethral Carcinoma: Update 2018

- Disease presentation in Males & Females
 - Incidence, Risk Factors, Location, Histologic types
- Evaluation, Staging & Natural History
 - MRI
- Treatment & Prognosis- Males & Females
 - Location
 - Stage
 - Multimodal Strategies in Advanced disease

Urethral Carcinoma⁽¹⁻³⁾

- Incidence⁽¹⁾**
 - 1973-2002, approx. 1615 cases
 - Males-4.3/million
 - Females- 1.5/million
 - Increases with age
- Age^(2,3)**
 - Males 59 (36-92)
 - Females 60 (21-84)
- Racial Predisposition⁽¹⁾**
 - More common among African Americans

1) Swartz et al. Al. Urology 68: 1164, 2006
2) Dalbagni et al. Urology 53: 1999
3) Dalbagni et al. Brit J Urol 82: 1998

Urethral Carcinoma Associated Factors

- Male**
 - Stricture (25-76%)
 - Sexually transmitted disease (24-50%)
 - HPV infection (29%)
 - Trauma (7%)
- Female**
 - Chronic irritation (caruncles, fibrosis, polyps, HPV infection)
 - Sexual activity
 - Diverticula

Inflammation is a common theme

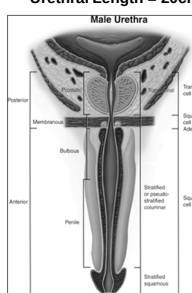
1) Terry et al. Principles & Practice Genitourinary Oncology. Lippincott-Raven, 1997
2) Dalbagni et al. Urology 53: 1999
3) Wiener et al. Cancer Res 52: 1992, Derksen et al. World J Urol 31: 2013

Urethral Carcinoma Pathology & Site of Origin

Males

- Site**
 - Bulbo membranous (25-59%)
 - Anterior (33-39%)
 - Prostatic (38%)
- Pathologic types**
 - Squamous (63-80%)
 - Urothelial (20-33%)
 - Adenocarcinoma (<5%)
 - Other (<2%)

Urethral Length = 20cm



Srinivas & Kahn. Int Urol Nephrol 20:1988
Dalbagni et al. Urology 53:1999
Palmer & McCullough. Adult & Pediatric Urology. Mosby Yearbook, St. Louis, 1981
Gakis et al. World J Urol. doi:10.1007/s00345-015-1583-7 Figure from Campbell's Urology

Urethral Carcinoma Pathology & Site of Origin

Females

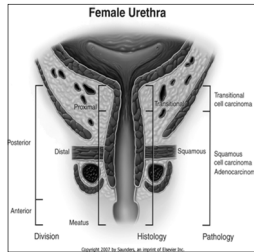
• Site

- Distal (35-69%)
- Whole (38-43%)
- Proximal (9-28.9%)

• Histology

- Squamous (19-70%)
- Urothelial (12-45%)
- Adenocarcinoma (15-35%)
- Other (1-3%)

Urethral Length =4cm



Grabstald Cancer 32:1973
Srinivas & Kahn. Int Urol Nephrol 19:1987
Weghaupt et al. Gynecol Oncol 17:1984
Figure from Campbell's Urology

Dalbagni et al. Brit J Urol 82:1998 Derksen et al. World J Urol 31: 2013
Grigaby. Int J Radiation Oncol Biol Phys 41:1998
Gakis et al. World J Urol: doi:10.1007/s00345-015-1583-7

Urethral Carcinoma Clinical Manifestations

Male

- Obstruction 43%
- Irritative Symptoms 20%
- Hematuria 17%
- Mass 28%
- Abscess 20%
- Discharge 4%
- Incidental 4%

Median Time to Presentation – 7.5 mos

Dalbagni et al. Urology 53: 1999, 46 patients 1958-1996

Urethral Carcinoma Clinical Manifestations

Female

- Irritative 41%
- Spotting 35%
- Obstructive 28%
- Hematuria 23%
- Mass 20%
- Discomfort 13%
- Discharge 7%
- Incidental 2%

Median Time to Presentation – 4.5 mos

Dalbagni et al. Brit J Urol 82: 1998 72 patients 1958-1994

Urethral Carcinoma Evaluation

- Examination Genitalia
 - Protruding lesions
 - Prolapse, caruncles, benign or malignant tumors
 - Palpable Masses
 - Diverticuli, abscess, tumors
- Inguinal Examination
 - Palpable adenopathy usually related to metastasis
- Cystourethroscopy with biopsy, vaginoscopy
 - Multiple sites along urethra
 - Exam under anesthesia
- MRI to define soft tissue detail
- CT scan abdomen, CXR



Hopkins & Grabstald. Campbell's Urology 9th Ed. W.B. Saunders, 1986
NCCN Guidelines Version 1.2018, Dayyani et al. BJU 2014

Urethral Cancer TNM Staging System

Table 5. American Joint Committee on Cancer (AJCC)
TNM Staging System for Urethral Carcinoma (8th ed., 2017)

Male Penile Urethra and Female Urethra

T	Primary Tumor	N	Regional Lymph Nodes
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
Ta	Non-invasive papillary carcinoma	N1	Single regional lymph node metastasis in the inguinal region or true pelvis (perivascular, obturator, internal (hypogastric) and external iliac), or presacral lymph node
Tis	Carcinoma in situ	N2	Multiple regional lymph node metastasis in the inguinal region or true pelvis (perivascular, obturator, internal (hypogastric) and external iliac), or presacral lymph node
T1	Tumor invades subepithelial connective tissue	M	Distant Metastasis
T2	Tumor invades any of the following: corpus spongiosum, perineural muscle	M0	No distant metastasis
T3	Tumor invades any of the following: corpus cavernosum, anterior vagina	M1	Distant metastasis
T4	Tumor invades other adjacent organs (e.g., invasion of the bladder wall)		

Prostatic Urethra

T	Primary Tumor	G	Histologic Grade (G)
TX	Primary tumor cannot be assessed		Grade is reported by the grade value. For urethral histology, a low- and high-grade designation is used to match the current WHOISUP recommended grading system.
T0	No evidence of primary tumor		
Ta	Non-invasive papillary carcinoma	LG	Low grade
Tis	Carcinoma in situ involving the prostatic urethra or perineural or prostatic ducts without stromal invasion	HG	High grade
T1	Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium		For squamous cell carcinoma and adenocarcinoma, the following grading schema is recommended:
T2	Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urethral surface or by invasion from prostatic ducts	GX	Grade cannot be assessed
T3	Tumor invades the periprostatic fat	G1	Well differentiated
T4	Tumor invades other adjacent organs (e.g., extraprostatic invasion of the bladder wall, rectal wall)	G2	Moderately differentiated
		G3	Poorly differentiated

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

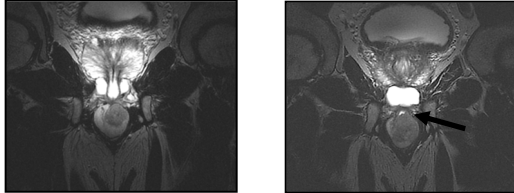
Male Urethral CA-LJ Pretherapy

- Sagittal T2 weighted image with tumor involving the corpus spongiosum.
- The prostatic urethra is dilated (yellow)



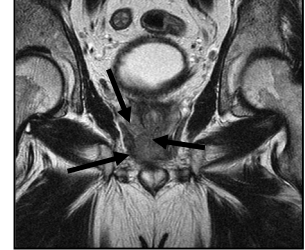
MALE URETHRAL CA- LJ Pretherapy- Stage T3?

- Coronal T2 weighted images. Tumor involves the corpus spongiosum. Superior border of the bulb (and hence UGD is likely) involved.



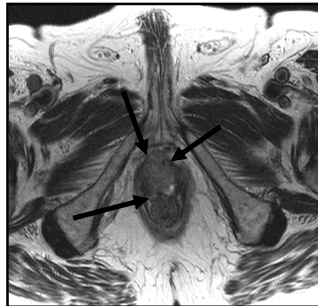
MALE URETHRAL CA-CN Pretreatment Stage T4

- T2 weighted Coronal image shows mass (yellow) extending to the right side of the prostate gland and involving the right levator anus muscle (white).



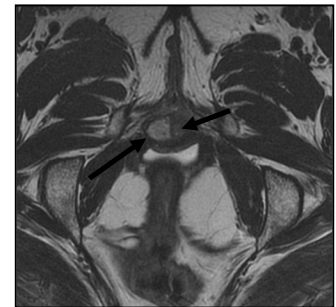
MALE URETHRAL CA-CN Pretreatment Stage T4

- T2 weighted Coronal image above the level of the UG diaphragm shows mass (yellow) extending posterior to involve the anterior wall of the rectum (white)



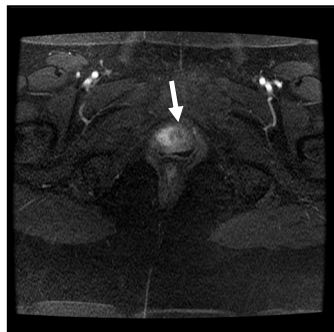
Female Urethral - CA Pretreatment - LJ

- Axial T2. Vagina distended with gel.
- Urethra (yellow)
- Tumor in diverticulum (white)



FEMALE URETHRAL CA-LJ

- Axial T1 post contrast
- Tumor enhancing (yellow)



Female Urethral CA-LJ Stage T2

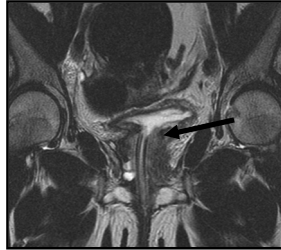
- Sagittal T2. Tumor in distal urethra (yellow)
- Vagina and bladder wall not involved



Female Urethral CA-BB Pretreatment Stage T3



Sagittal T2. Mass in urethra involving bladder neck



Coronal T2. Mass involving bladder neck

Urethral Carcinoma Natural History

Primary Tumor

• Local growth and extension

• Males

- Corpus spongiosum, cavernosum
- GU Diaphragm, levator muscles, prostate, scrotum, rectum

• Females

- Corpus Spongiosum, vagina, bladder
- Levator muscles

Sharp & Angemeier: Tumors of the Urethra-Campbell-Walsh Urology 11th ed Elsevier 879, 2016

Urethral Carcinoma Natural History

Metastasis

• Regional Lymph Nodes @ Presentation

- Males (14-30%)
- Females (21-28%)
- Distal, pendulous tumors → Inguinal nodes
- Proximal, bulbomembranous tumors → Pelvic Nodes

• Distant Metastases

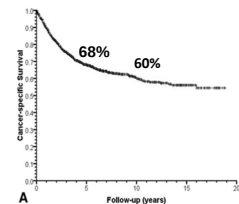
- @ presentation (rare, 0-19%)
- Post-therapy recurrence (30-40%)
 - Lung, liver, bone, lymph nodes, brain

Carroll. Current Genitourinary Cancer Surgery, Lea & Febiger, Philadelphia 1990
Kaplan et al. J Urol 98: 1967
Ray et al. J Urol 117: 1977
Gakis et al. World J Urol 34, 2016; Sharp & Angemeier: Tumors of the Urethra-Campbell-Walsh Urology 11th ed Elsevier 879, 2016

Male Urethral Carcinoma Treatment & Prognostic Factors

Determine Treatment

- Stage
- Location
- Histology



Prognostic Factors

- Stage, Grade, Surgery versus none

Dinney et al Urology 43: 1994

Rabbani et al Cancer 117: 2011 SEER Data 5.10 year Cancer specific survival N=2,065 patients

Male Urethral Carcinoma Survival According to Location⁽¹⁾

Urethral Location	No. Patients	Stages			Incidence Local Relapse (%)	Disease Specific Survival (%) (mos)	Mean F/U (mos)
		A-B	C	D1-D2			
Fossa	4 ⁽²⁾	3		1	0	100	93
Penile	11 ⁽³⁾	1	3	7	1/7 (14)	60	48
Bulbo-membranous	7 ⁽⁴⁾	2	2	4	4/7 (57)	29	31

(1) Dinney et al. Urology 43: 1994
(2) One patient received chemotherapy in addition to surgery
(3) Five patients surgery alone, 6 patients surgery and chemotherapy
(4) Chemotherapy & XRT – 2 patients
Exenteration + chemotherapy = 4 patients
Penectomy – 1 patient

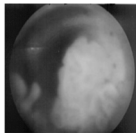
Male Urethral Carcinoma Treatment Options

- Anterior Urethra
 - Transurethral resection/fulguration
 - Excisions, penile conserving procedures
 - Partial or total penectomy
- Posterior Urethra
 - Transurethral resection – carefully selected patients
 - Exenterative surgery
 - *Multi-modal therapy favored*

Male Urethral Carcinoma Excision, Transurethral Resection (TUR)

- **Carefully Selected Patients!**
- **Excision**
 - Low grade, Low stage meatal lesions
- **TUR**
 - Low grade, stage, solitary lesions
 - Urothelial carcinoma most favorable histology $\pm$ BCG

FIG. 5. Endoscopic view of distal urethral papillary tumour (lower 6).



Zietman et al. Urol Clin N Am 19(2):1992
Konnack. J Urol 123:1980
Brettona and Herr. J Urol 141: 1989
Gillitzer et al BJU 100:2009

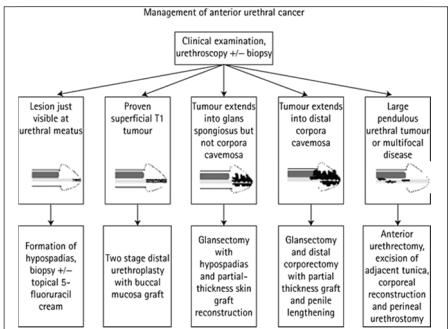
Penile-Preserving Surgery for Distal Urethral Carcinoma

- **Patient**
 - N=18
- **Location**
 - Glanular or penile
- **Procedures**
 - Penile preserving
- **Median Follow-up**
 - 20 mos (9-58)

Feature	Mean (range) or N
Age, years	57 (39-83)
Histological type:	
SCC	17
Mucoepidermoid	1
Tumour stage:	
Tis	2
T1	5
T2	3
T3	8
T4	0
N0	12
N+	6
Tumour grade:	
G5	2
G1	1
G2	7
G3	8
Clinical presentation	
Obstructive symptoms	7
Bloody discharge or haematuria	4
Urethrocavitaneous fistula	1
Mass	9
Meatal lesion	8
Palpable lymph nodes	5

Smith et al. BJU 100:82, 2007

Penile-Preserving Surgery for Distal Urethral Carcinoma



Smith et al. BJU 100:82, 2007

Penile-Preserving Surgery for Distal Urethral Carcinoma



Smith et al. BJU 100:82, 2007



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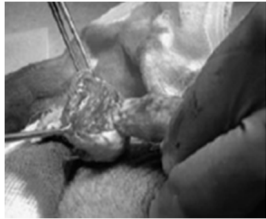
Campbell's Urology, 9th Edition, Saunders Elsevier, Philadelphia, PA, 2007

Penile-Preserving Surgery for Distal Urethral Carcinoma



Smith et al. BJU 100:82, 2007

Penile-Preserving Surgery for Distal Urethral Carcinoma:Glansectomy



Smith et al. BJU 100:82, 2007

Penile-Preserving Surgery for Distal Urethral Carcinoma

- NED 13/18 (78%)
- No local recurrences
- Deaths (4)
 - 2 nodal progression
 - 1 embolus
 - 1 unrelated, NED

Node type	1h targets	Adjusted treatment	Follow-up months	Outcome	
Hypothalamic and neural nuclei					
1633	CS	None	DSU	12	MS
1538	CS	None	MS, vestibular	26	MS
1630	CS	None	None	36	MS
1631	CS	None	None	36	MS
Two-stage distal orthogonality with BCM graph					
1446	CS/MS	Left IL	None	1 year post-operative at 41	MS
Quantitative and neuroanatomy					
1633	CS/MS	S/MS	None	23	MS
1417	CS/MS	S/MS	None	19	MS
1630	CS/MS	None	None	33	MS
Quantitative and neuroanatomy					
1673	CS/MS	S/MS	None	9	MS
1644	CS/MS	Left IL	None	36	MS
1636	CS/MS	None	None	36	MS
Quantitative, distal orthogonality and neuroanatomy					
1633	CS/MS	None, post-op IL	None	23	MS
1678	CS/MS	S/MS, bilateral frontal lobe resect	None	12	MS
1634	CS/MS	S/MS	HE/MS/VS	8	Dist MS
1678	CS/MS	S/MS	None	12	MS
1679	CS/MS	Left, right and 4th p. resect.	HE	Anterior IL at 21	Lost to follow-up
1678	CS/MS	Left, right and 4th p. resect.	None	46	MS
Anterior orthogonality, adjusted treatment, personal orthogonality					
1538	CS/MS	Left IL	HE/MS/VS	18	Dist MS
1630	CS/MS	Left IL	HE	Anterior IL at 42	Following treatment

Smith et al. BJU 100:82, 2007, Median follow-up 20.5 mos (9-58)

Male Urethral Carcinoma Survival (%)

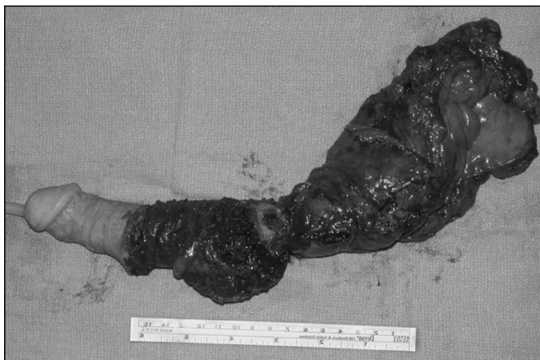
Series	Year	Stage			Location			Follow-up	
		Low	High	pValue	Distal	Proximal	pValue	Overall	(mos)
Dinney et al. ⁽⁴⁾	1979-90	67-100	33-44 ⁽⁸⁾	N.S.	60	29	NS	52 ⁽⁷⁾	50 ⁽⁴⁾
Dalbagni et al. ⁽²⁾	1958-96	83	36	0.07	69	26	0.03	42 ⁽⁶⁾	125
Thyaviljalry ⁽³⁾ et al.	1988-2001	67	33	0.001	72	36	0.02	49 ⁽⁶⁾	48

- (1) Urology 43(4):506, 1994
- (2) Urology 53:1126, 1999
- (3) Int J Urol 13:716, 2006
- (4) Mean Follow-up
- (5) Stages A-B
- (6) Stages C-D
- (7) Disease Specific
- (8) Overall Survival

Male Advanced Urethral Carcinoma Local Recurrence

Series	Patients No.	Pendulous No. (%)	Bulbo Membranous No. (%)	Overall No. (%)
Dinney et al. ^[1]	23 ^[1]	1/13 (8)	4/7 (57)	5/20 (25)
Dalbagni et al. ^[2]	46	6/18 (33)	14/28 (50)	20/46 (43)

- (1) Dinney et al. Urology 43:506, 1994 – Local therapy attempted in 20/23 patients mean follow-up = 50 mos.
(2) Daibagni et al. Urology 53: 1126, 1999 – Median follow-up = 125 mos.



Zeidman et al: Urol Clin N Am 19:359, 1992

Male Posterior Urethral Carcinoma Local Recurrence and Extent of Surgery

Procedure	Series	No. Recurrence / Total
Exenteration +/- node dissection ⁽¹⁾	Lupo et al. ⁽¹³⁾	2/7
	Bay et al. ⁽¹⁴⁾	7/9
	Bracken et al. ⁽¹⁵⁾	2/2
	Dinney et al. ⁽¹⁴⁾	1/1
	TOTAL	12/19 (63)
Exenteration en bloc pubectomy +/- node dissection +/- xrt ⁽²⁾	Klein et al. ⁽⁷⁾	2/7
	Sauntleworth et al. ⁽¹⁶⁾	0/4
	Bracken et al. ⁽¹⁶⁾	0/3
	Dinney et al.	2/3
	TOTAL	4/17 (24)

- (1) Penectomy, urethrectomy, cystoprostatectomy +/- pelvic +/- inguinal dissection, ileal conduit diversion.
(2) Above and en bloc removal of pubis and urogenitourinary diaphragm
(3) Urology 24:527, 1984 (4) J Urol 117:591, 1977 (5) Southern Med Journal 23:1003, 1980
(6) Urology 43:506, 1994 (7) Cancer 51:1238, 1983 (8) BJU 41:739, 1969 (9) Urol 29:248, 1982

Male Urethral Carcinoma Radiation Therapy

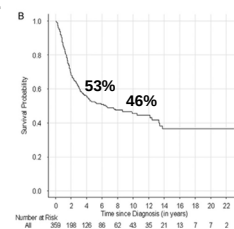
- **Poor Local Control**
 - Anterior tumors, 0-25% five year survival
 - Posterior tumors – only anecdotal survivors
- **Complications**
 - Stricture
 - Chronic Edema
 - Necrosis
 - Fistula

Kaplan et al. J Urol 98:1967
Hopkins & Grabstald: Campbell's Urology. W.B. Saunders, 1986
Zietman et al. Urol Clin N Am 19:1992
Dalbagni et al. Urology 53:1126,1999
Bracken et al. Southern Med Journal 73:1003,1980

Female Urethral Carcinoma Treatment and Prognostic Factors

Determine Treatment

- Stage
- Location
- Histology



Prognostic Factors

- Age, Race, Stage, Histology, Size, Surgery versus None

Grigsby. Int J Radiat Oncol Biol Phys 41:1998; Champ et al. Urology 80: 2012- SEER Data 5,10 year Cause specific survival, N=722 patients ;Dalbagni et al. Brit J Urol 82:1998 ; Garden et al. cancer 73:1993; Bracken et al. J Urol 116:1976
Milosevic et al. Radiotherapy and Oncology 56:2000

Female Urethral Carcinoma Treatment Options

Tis, T1, Small T2

- Transurethral resection
- Distal urethrectomy
- Radiation therapy

T2-T4

- Exenterative surgery
- Radiation
- *Multimodal therapy favored*

Female Urethral Carcinoma Surgery ± Radiotherapy: Low Stage Tumors⁽¹⁾

Treatment	Series	No. Pts.	Survival (%)	Follow-Up Period
Surgery ⁽²⁾	Bracken et al. ⁽⁴⁾	3	1/3 (33)	96 months
	Grabstald ⁽⁵⁾	10	8/10 (80)	5 years
	Herr ⁽⁶⁾	24	20/24 (83)	5 years
	DiMarco ⁽⁹⁾	27	NS (80)	5 years
Surgery + XRT ⁽³⁾	Bracken et al. ⁽⁴⁾	8	5/8 (63)	53 months
	Grabstald ⁽⁵⁾	3	2/3 (67)	5 years
	Hahn ⁽⁷⁾	1	1 (100)	5 years
	Ali ⁽⁸⁾	1	1 (100)	48 months
AVE			38/50 (76)	

(1) Stage 0-A (5) Cancer 32: 1973
(2) Excision, TUR, Distal Urethrectomy (6) Campbell's Urology 7th Edition W. B. Saunders, Philadelphia 1998
(3) Surgery and Adjuvant Radiation (7) Urology 37: 1991
(4) J Urol 116: 1976 (8) Cancer 62: 1998
(9) Urologic Oncol 22: 2004

Female Urethral Carcinoma Low Stage: Radiotherapy⁽¹⁾

Series	No. Patients	Treatment	5- Year Survival (%)
Grabstald ⁽¹⁾	11	XRT + Implant	3/11 (27)
Delclos ⁽²⁾	11	XRT + Implant	6/11 (55)
Taggart ⁽³⁾	15	XRT + Implant	8/15 (53) ⁽³⁾
Johnson & O'Connell ⁽⁴⁾	5	XRT + Implant	3/8 (60) ⁽⁴⁾
Chu ⁽⁵⁾	11	XRT + Implant	7/11 (64)
Weghaupt ⁽⁶⁾	42	XRT + Implant	30/42 (77)
Pointon ⁽⁷⁾	26	XRT + Implant	20/26 (77) ⁽⁷⁾
Prempre ⁽⁸⁾	6	XRT + Implant	6/6 (100)
Antoniades ⁽⁹⁾	8	Implant Alone	8/8 (100) ⁽⁹⁾
Milosevic ⁽¹⁰⁾	14	XRT + Implant	10/14 (71) ⁽¹⁰⁾
Ave			101/152 (66)

(1) JAMA 197: 1966 (6) Gynec Oncol 37: 1984
(2) Textbook of Radiotherapy, Lea & Febiger, Philadelphia, 1960 (7) Brit J Urol 40: 1968, 3 year survival
(3) Roentgen. Amer J 114: 1972 – 2 year survival (8) Cancer 54: 1984
(4) Urology 21: 1983, 4 year NED survival (9) Cancer 54: 1969, 1 patient dead at 3 years
(5) Radiotherapy 197: 1973 (10) Radiotherapy & Oncology 56: 2000, 7 year cause specific survival

Female Urethral Carcinoma Tumor Size & Survival

Series	No. Patients	Treatment	Survival (%)		
			<2 cm	2-4 cm	>4cm
Bracken ⁽¹⁾	68	Surgery/XRT	60	46	13
Grigsby ⁽²⁾	44	Surgery/XRT	89	36	19
Milosevic ⁽³⁾	34	XRT Alone	78	75	12

(1) J Urol 116: 1976 – Overall survival-categories <2 cm, 2-4 cm, ≥5 cm @ 5 years
(2) Int. J Radiat Oncol Biol Phys 41: 1998 – Disease specific survival @ 5 years
(3) Radiotherapy and Oncology 56: 2000 – Disease specific survival, categories <2 cm, 2-4 cm, ≥4 cm @ 7 years

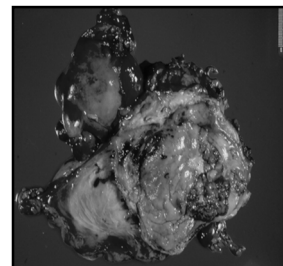
Female Urethral Carcinoma Influence of Tumor Site & Stage⁽¹⁾

	No. Pts.	Percent Survival @ 5 Years		
		Disease Specific	Local Rec Free	Met Free
Site				
Anterior	25	69	53	71
Posterior	13	46	42	48
Entire	27	18	32	24
Stage				
Low ⁽²⁾	12	89	83	88
High ⁽³⁾	49	33	33	36

- (1) Dalbagni et al. Brit J Urol 82: 1998, 72 patients treated with surgery, radiation or both
(2) T0-T1
(3) T2-T4

Female Urethral Carcinoma Exenteration Alone: Advanced Tumors*

- 5 year survival⁽¹⁻⁴⁾
– (11-21%)



- (1) Srinivas & Kahn. Int J Urol Nephrol 19:1987
(2) Peterson et al. J Urol 110:1973
(3) Desai et al. J Urol 110:1973
(4) Grabstald. Cancer 32:1973
* Stage pT3-4

Female Urethral Carcinoma Radiotherapy: Advanced Tumors

Series	No. Patients	5-Year Survival No.	(%)
Delclos et al ⁽¹⁾	25	7	(28)
Weghaupt et al ⁽²⁾	20	10	(50)
Grabstald et al ⁽³⁾	19	1	(5)
Antoniades ⁽⁴⁾	11	4	(36)
Hahn et al ⁽⁶⁾	8	3	(38)
Chu ⁽⁷⁾	8	0	(0)
Total	98	29	(30)

- (1) Textbook of Radiotherapy. Lea & Febiger, Philadelphia 1980
(2) Gynecol Oncol 17: 1984
(3) JAMA 197: 1966
(4) Cancer 24: 1969
(5) Cancer 54: 1984
(6) Urology 37: 1991
(7) Radiology 107: 1973

Female Urethral Carcinoma Preoperative XRT & Surgery: Advanced Tumors

Series	No. Patients	No. Alive (%)	Follow-Up Period
Grabstald ⁽¹⁾	20	5 (25)	5 years
Ali et al ⁽²⁾	5	1 (20)	54 months
Johnson ⁽³⁾ & O'Connell	7	3 (43)	1, 1, 12 mos.
Herr ⁽⁴⁾	39	21 (54)	5 years

- (1) Cancer 32: 1973
(2) Cancer 62: 1988
(3) Urology 21: 1983
(4) Campbell's Urology 7th Edition. W. B. Saunders, Philadelphia 1998

Female & Male Urethral Carcinoma Multimodal Therapy: Advanced Tumors

Series	No. Patients	Tumor Stage	# Alive NED (%)	Survival Mos. (Range)
Concurrent Chemo/ 7 Radiation ^(1,2)	7	T2-T3, Nx-N2	4/7 (57)	60 (10-98)
Chemotherapy & Surgery ⁽³⁾	6	C-D2	5/6 (83)	79 (16-156)
Concurrent chemo /Radiation & Surgery ^(1, 4)	7	T3-T4, N0-N2	5/7 (71)	30 (7-48)

- (1) Gheller et al. Urology 52: 1998, 5-FU, Cisplatin, MVAC, 70-75 Gy Tumor, Nodes, Exenteration
(2) Licht et al. J Urol 153: 1995, 5-FU, Mitomycin C, 30-50 Gy pelvis
(3) Dinney et al. Urology 43: 1994 - Surgical resection to remove all gross disease, multiple chemotherapy regimens
(4) Johnson et al. J Urol 1989, 5-FU, Mitomycin, 40 Gy pelvis perineum, exenteration

Advanced Urethral Cancer Cisplatin Based Chemotherapy Patient Characteristics

Table 1 Patients' characteristics		
Characteristic	Number of patients	Percentage
Median age 66.5, years (36-81)		
Race		
White	23	52
Black	14	32
Other	7	16
Female gender	28	64
Histologic subtype		
SCC	17	39
Adenocarcinoma	13	30
Total UC	8	19
UC	4	9
Papillary UC	2	5
Mixed morphology, SCC, and UC	2	5
Undifferentiated carcinoma	5	11
Other	1	2
N stage		
N0	18	41
N1	19	43
M1	7	16
T stage		
T1-2	1	2
T3-4	43	98

SCC = squamous cell carcinoma; UC = urothelial carcinoma.

Dayyani et al. Urol Oncol. 31:1171-2013-44 Patients with advanced primary urethral carcinoma eligible for chemotherapy

Advanced Urethral Cancer Cisplatin Based Chemotherapy

- Based on histologic subtype
 - Squamous cell carcinoma
 - Cisplatin, Gemcitabine, Ifosfamide (CGI, 85%)
 - Paclitaxel, Ifosfamide, Cisplatin (TIP, 15%)
 - Adenocarcinoma
 - Gemcitabine, 5 Fluorouracil, Leucovorin, Cisplatin (GEM-FLP)
 - Urothelial carcinoma
 - Methotrexate, Vinblastine, Doxorubicin, Cisplatin (MVAC), CGI or TIP

Dayyani et al. Urol Oncol. 31:1171,2013

Advanced Urethral Cancer Cisplatin Based Chemotherapy

Table 2
Response rates to platinum-containing chemotherapy regimens*

Regimen	Complete response no. (%)	Partial response no. (%)	Minor response no. (%)	Stable disease no. (%)	Progressive disease no. (%)
CGI	2 (11)	12 (63)	2 (11)	3 (16)	0
Gem-FLP	1 (11)	5 (56)	0	2 (22)	1 (11)
ITP	1 (25)	2 (50)	1 (25)	0	0
MVAC	1 (50)	1 (50)	0	0	0
Other	0	1 (50)	1 (50)	0	0
Total	5 (14)	21 (58)	4 (11)	5 (14)	1 (3)

CGI = cisplatin, gemcitabine, and ifosfamide; Gem-FLP = cisplatin, gemcitabine, 5-fluorouracil, and leucovorin; ITP = ifosfamide, paclitaxel, and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin.
*Thirty-six patients received a platinum-containing regimen.

Dayyani et al. Urol Oncol. 31:1171,2013, CR +PR =72%

Advanced Urethral Cancer Cisplatin Based Induction Chemotherapy and Surgery

- Total patients
 - N = 20
- Median survival = 26 mos (2.3-55.7)
- 10/20 (50%) alive median 42 mos
- Local recurrence
 - N = 3 (15%)
- Lymph node metastases
 - N=4/9 (44%) disease free > 3 years

Dayyani et al. Urol Oncol. 31:1171,2013

Coordinated Chemoradiation Therapy With Genital Preservation for the Treatment of Primary Invasive Carcinoma of the Male Urethra

Michael S. Cohen, Veronica Triaca, Brian Billmeyer, Robert S. Hanley, Lyubov Girshovich,
Todd Shuster, Richard A. Oberfield and Leonard Zinman*

From the Departments of Urology (MSC, VT, BB, RSH, LZ), Oncology (TS, RAO) and Radiation Oncology (LG), Lahey Clinic Medical Center, Burlington, Massachusetts

	No. Pat (%)
Median age (range)	58 (39-87)
Presenting symptoms:	
Stricture	13 (72)
Mass/penile lesion	6 (33)
Prior urethroplasty	4 (22)
Pain	3 (17)
Hematuria	2 (11)
LUTS	2 (11)
Phimosis	1 (6)
Clinical stage:	
T2N0	2 (11)
T3N0	8 (44)
T4N0	2 (11)
T4N1	1 (6)
T4N2	5 (28)
Tumor urethral location:	
Pendulous	9 (50)
Bulbomembranous	9 (50)
Intracavitary	17 (90)
SCU	1 (6)
Grade:	
Well differentiated	1 (6)
Moderately differentiated	7 (39)
Poorly differentiated	10 (56)

Cohen et al. J Urol 179:536-41, 2008, 18 patients treated with induction chemo-radiation based treatment

Male Advanced Urethral Cancer Chemoradiation: Treatment

- XRT
 - 45-55 Gy in 25 fractions over 5 weeks
 - Inguinal, pelvic nodes, and primary tumor
 - 12-15 Gy boost to primary
- Chemotherapy
 - Concurrent with XRT
 - 5 Fluorouracil
 - IV Infusion D1-4, 29-32
 - Mitomycin
 - IV bolus D1 and 29

Cohen et al. J Urol 179:536-41, 2008

Male Advanced Urethral Cancer Chemoradiation: Longterm Follow-up

- Patients
 - N=26
- Median Follow-up
 - 35.5 mos (4-264)
- Complete Clinical Response
 - 19 (79%)
 - 42%, disease recurrence, median 12.5 mos
- No Response
 - 5 (21%), DOD

Kent et al. J Urol 193:532, 2015

Male Advanced Urethral Cancer Chemoradiation: Longterm Follow-up

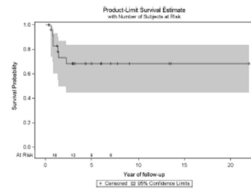


Figure 3. Disease specific survival

5 year DSS -68%

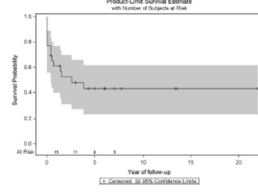


Figure 4. Disease-free survival

5 year DFS =43%

Kent et al. J Urol 193:532, 2015, 6 patients underwent salvage surgery, 8/15 longterm survivors (53%) required urethroplasty

Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: results of the international collaboration on primary urethral carcinoma

G. Gakis^{1*}, T. M. Morgan², S. Daneshmand³, K. A. Keegan⁴, T. Todenhöfer¹, J. Mischinger¹, T. Schubert¹, H. B. Zaid¹, J. Hirsoski⁵, B. Ali-Ei-Deir⁶, R. H. Clayman⁷, S. Galland⁸, K. Ougbade⁹, M. Rink⁹, H.-M. Fritsche⁹, M. Burger⁹, S. S. Chang¹, M. Babjuk⁹, G. N. Thalmann¹⁰, A. Stenzl¹ & J. A. Elstathiou⁷

Clinical $\geq$ cT3 or N+ primary urethral cancer (N=26)

- Neoadjuvant Chemotherapy(NAC) or Chemoradiation(N-CRT) (8)
- Surgery $\pm$ adjuvant chemotherapy(ACH) (18)

Overall Survival @ 3 years (p=0.016)

- NAC 100%
 - N=5
- N-CRT 100%
 - N=3
- Surgery alone 50%
 - N=10
- Surgery+ACH 20%
 - N= 8

Predictors of Survival

- Neoadjuvant therapy (p=0.022)
- Posterior tumor location (p=0.005)

Ann Oncol 26: 1754,2015- 10 institutions including 124 patients

Male Urethral CA-LJ Pre/Post Treatment*



cT3N1 M0 SCC

pT0N0!

The tumor is smaller and has a dark signal of T2 weighted sequences indicating likely post treatment fibrosis.

*CGI,GA, neoadjuvant concurrent 5-FU, Mito, XRT 48Gy urethra, inguinal, pelvic nodes, surgical resection. NED @ 5 years

Female Urethral CA-MP Pre/Post Therapy*



Axial T2. Mass in urethral diverticulum
T2,N0- Clear Cell Adeno Ca

Empty diverticulum (yellow)
from 2 o'clock of urethra

TMP/TAMVAC, XRT 68 Gy urethra, inguinal, pelvic nodes- NED @ 7 years

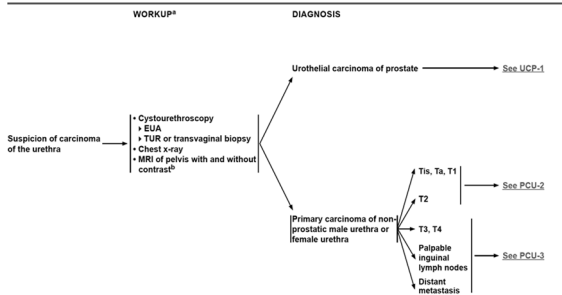
Urethral Carcinoma Update 2018:Conclusions

- **Therapy & Prognosis**
 - **Extent of Disease**
 - Size
 - Location
 - T Stage
 - **Presence, absence metastasis**
 - **MRI important!**
- **Low Stage, Distal Lesions**
 - **Male**
 - Surgical therapy-Penile Preservation feasible
 - **Female**
 - Surgery alone
 - Surgery & Radiotherapy

Advanced Urethral Cancer Update 2018: Conclusions

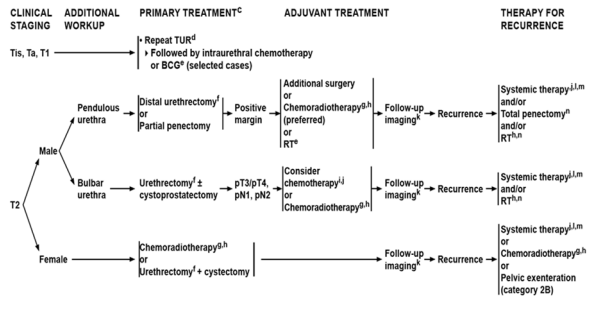
- **Multidisciplinary approach is critical**
 - Loco-regional control paramount!
 - Distant metastases uncommon @ presentation
- **Chemotherapy, radiation and surgery play important roles**
 - Optimal induction chemotherapy regimen has yet to be defined
 - Adenocarcinoma, squamous, urothelial histologies respond to cisplatin based agents
 - Adjunct to radiotherapy (neoadjuvant, concurrent)
 - Surgical resection with negative margins
 - Post chemotherapy or XRT associated with highest rates of local control and survival
 - Morbid
 - Concurrent Chemoradiation
 - Activity in squamous histology
 - Evolving role in achieving local control with organ preservation
- **Multi-Institutional clinical Trials Imperative !**

Urethral Cancer: NCCN Treatment Guidelines 5.2018



NCCN Clinical Practice Guidelines(2018)-http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

Urethral Cancer: NCCN Treatment Guidelines 5.2018



NCCN Clinical Practice Guidelines(2018)-http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

DISORDERS OF THE SCROTUM AND SEMINAL VESICLES



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Disclosure Statement

REPORTS NO COMMERCIAL INTEREST

Objectives

- Review common scrotal disorders and the surgical treatment for them
- Understand the indications for scrotal surgery, as well as the complications
- Understand embryology and anatomy of the seminal vesicles (SV) and how this impacts clinical picture
- Review indications and techniques for SV surgery

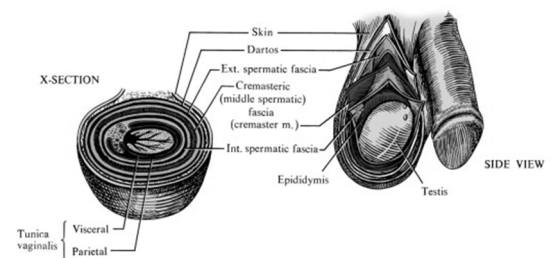
Outline for Scrotal Topics

- Anatomy
- Common diagnoses
 - Vasectomy
 - Hydrocele
 - Spermatocoele
 - Orchalgia
- Surgery
- Outcomes/Complications

Anatomy of the scrotum

- Tissue layers
 - Scrotal skin
 - Dartos-continuous with Colles, Scarpa, and the dartos fascia of the penis
 - Tunica vaginalis
- These layers form anatomic barriers to the spread of infection, particularly necrotizing fasciitis
- The testes and epididymides tend to be spared from necrotizing fasciitis of the scrotum

Scrotal Tissue Layers



Adapted from Campbell's Urology

Anatomy of the Scrotum

- ⦿ Important to understand blood supply of the scrotal contents
- ⦿ *Testis*
 - Testicular (internal spermatic) artery (main blood supply)
 - Deferential artery from internal iliac –superior
 - Cremasteric (external spermatic) artery from inferior epigastric artery
- ⦿ *Epididymis*
 - Superior epididymal artery derived from testicular artery
 - Inferior epididymal artery derived from deferential artery
- ⦿ *Vas deferens*
 - Seminal vesicle end: deferential artery
 - Testicular end: deferential artery and inferior epididymal artery

General Preop Principles

- ⦿ Scrotum fairly resilient, heals well in the absence of infection, chronic irritation
- ⦿ Typically, preop antibiotics not required unless pt at risk (DM, advanced age, poor nutrition, etc)
- ⦿ Recommended antibiotic 1st gen cephalosporin or clindamycin (if allergic)
- ⦿ Clipping/shaving should be done either day of procedure or in the OR

General Post op Principles

- ⦿ Compressive dressing prevents swelling, minor bleeding
- ⦿ Will not prevent hematoma from inadequate hemostasis
- ⦿ Post op antibiotics not typically necessary unless grossly infected tissue present
- ⦿ To drain or not to drain, that is the question...

Common Scrotal Conditions

- ⦿ Vasectomy
- ⦿ Hydrocele
- ⦿ Spermatocele
- ⦿ Chronic orchalgia

Vasectomy

- ⦿ Recent AUA Guidelines updated recommendations
- ⦿ Pre-procedural counseling recommended
- ⦿ Minimally invasive technique should be used to isolate the vas
- ⦿ Vasal occlusion with cautery and fascial interposition are recommended
 - Optional techniques acceptable if personal failure rates are low
- ⦿ Pathology specimen NOT recommended

Counseling

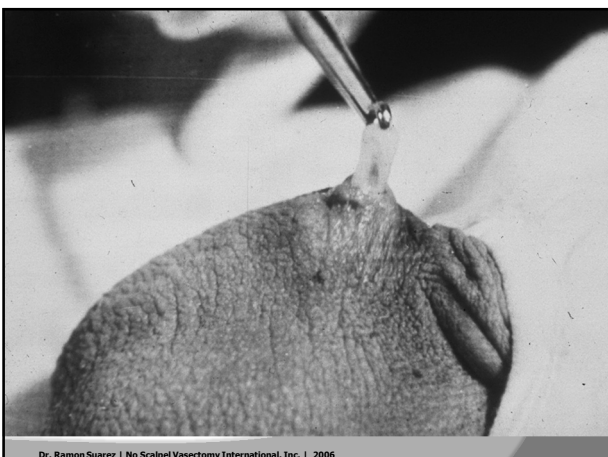
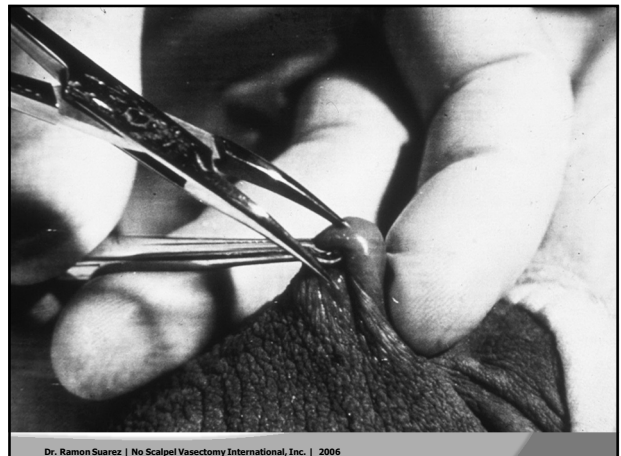
- ⦿ At a minimum, there should be some type of pre-vasectomy evaluation
- ⦿ This can be performed in person (preferably), electronically, or over the phone; scheduling pts without any type of evaluation is not recommended.
- ⦿ Ideally, the pt would also be examined prior to procedure to identify any confounding factors

Pre-vasectomy counseling

- ◎ Patients should understand:
 - Intended to be permanent
 - Not immediate
 - Known failure rate (1:2000)
 - Complication rate is low (~1-2%)
 - Do not need to discuss risks of CaP, etc
- ◎ Other forms of contraception should also be mentioned (both permanent and temporary) when applicable

Isolation and Delivery of the Vas

- ◎ Isolate the vas
- ◎ Grasp only the vas
- ◎ Separate vas from surrounding structures, including vasal vessels
- ◎ Perform minimally invasive technique (<10 mm) to access vas only
- ◎ NSV instruments ideal for this



Procedure

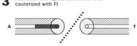
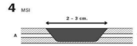
- ◎ Occlusion technique
 - Intra-luminal cautery-most effective
 - Fascial interposition-has been shown to reduce recanalization
- ◎ Therefore, the evidence shows that mucosal cautery, with or without FI, is the most effective occlusion technique



AUA Vasectomy Guideline 2012 - Statement 7

Key Concepts: RECOMMENDED Occlusion Techniques

Recommendation (Evidence Strength Grade C)

Occlusion Technique	# of Study Arms	# of Pts.	Occlusion Failure Rate
1 MC with FI 	13	18,456	0.0-0.55%
2 MC without FI 	5	13,758	0.0-0.60%
3 Open ended with FI 	4	4,600	0.0-0.50%
4 Marie Stopes 	1	48,814	0.64%

MC = Mucosal Cautery FI = Fascial Interposition

AUA Vasectomy Guideline 2012 - Statement 8

Key Concepts – Optional Occlusion Techniques

(Evidence Strength Grade C)

Occlusion Technique	# of Study Arms	# of Patients	Occlusion Failure Rate
5 Ligation both ends without FI 	31	24,797	0.0-13.79%
6 Ligation both ends with FI 	9	2,782	0.0-5.85%
7 Clips both ends without FI 	7	4,337	0.0-8.67%

These are optional techniques for surgeons whose training and/or experience indicate consistently acceptable failure rates

Post op recommendations

- Check post vasectomy SA 8-12 weeks (early recanalization can occur within first 6 weeks)
- Patient is considered sterile if there are no sperm or rare, non-motile sperm on a fresh, unspun sample
- If sample is not fresh and sperm are present, motility cannot be commented upon

Complications

- Rare (~1-2%), include hematoma, infection, chronic testicular pain
- Sperm granuloma may occur, especially if open-ended vasectomy performed
- Not a complication unless symptomatic
- Failure (ie, pregnancy) following confirmation of sterility ~1:2000

Hydrocele

- Typically a painless swelling of the scrotum
- Represents build up of fluid in the space between the parietal and visceral layers of the tunica vaginalis
- May be caused by lymph overproduction, decreased reabsorption, or a combination
- Often, history of scrotal, inguinal, or lower abdominal surgery, trauma, or inflammation
- Rarely, hydrocele can be presenting sign of malignancy

Hydrocele

- Ultrasound imaging should be performed to rule out scrotal/testicular masses, as well as to assess whether or not loculations are present
- In adolescents/young adults, communicating hydrocele should be ruled out

Hydrocelectomy

- May use median raphe or transverse unilateral incision
- Care should be taken not to enter the hydrocele sac until it is fully dissected
- Sac is opened under direct vision and fluid is removed
- Sac is then opened completely to expose testis and associated structures

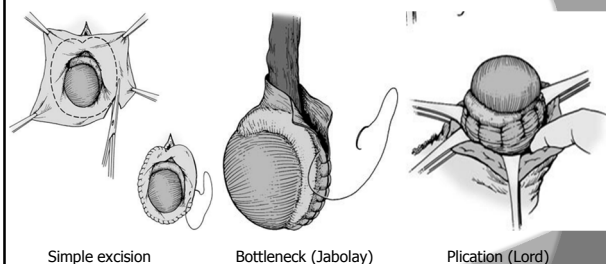
Hydrocelectomy

- Several methods for repair, including excision, bottleneck (Jaboulay), or plication (Lord)
- Simple excision best for very large, multiloculated, and/or thick-walled sacs
- Typically, 1 cm margin left after excision
- Edges should be oversewn to prevent bleeding

Hydrocelectomy

- Bottleneck procedure results in less bleeding, but must be sure not to constrict spermatic cord
- Plication best for thin-walled, small or moderate hydroceles.
- Has the lowest blood loss, although if sac is too big, may result in bunching of tissue

Hydrocelectomy techniques



Adapted from Campbell's Urology

Hydrocele-drain placement

- No good data regarding drain placement after scrotal surgery
- Does not appear to be a difference in complications based on drain
- Some patients may benefit
 - Complex scrotal surgery
 - Recurrent hydrocele
 - Excessive fluid production (ascites)
- Penrose for short term (1-2 d), closed system if longer

Complications of hydrocelectomy

- Typical scrotal surgery complications
 - Bleeding, infection
 - Prevented with meticulous hemostasis
- Recurrence
 - More common with plication, repeat procedures
- Injury to vas deferens/epididymis
 - Up to 10% of cases

Hydrocele aspiration/sclerosis

- Sclerotherapy best for small hydroceles in men where fertility is no longer desired
- Hydrocele aspirated with 16G angiocath
- 25 cc local anesthesia instilled
- Can use doxycycline, 95% EtOH, or any other sclerosant
- Significant rate of recurrence, may result in multiloculated hydrocele
- Can cause scarring of epididymis

Spermatocele

- Aneurysmal dilation of tubule within epididymis, typically in caput
- Does not represent an obstruction and only needs treatment if symptomatic
- Distinct from epididymal cyst, which is not connected to epididymal tubule
- Treatment may cause epididymal obstruction
- May recur (or develop anew), so consideration of epididymectomy in men not desired future fertility

Spermatocelectomy

- Incision similar to hydrocele
- Tunica vaginalis opened following delivery
- Once testis is delivered and exposed, tunica vaginalis over spermatocele is incised
- Spermatocele dissected away from epididymis down to neck entering tubule
- Ligated with small non-reactive suture to prevent further epididymal scarring

Spermatocelectomy

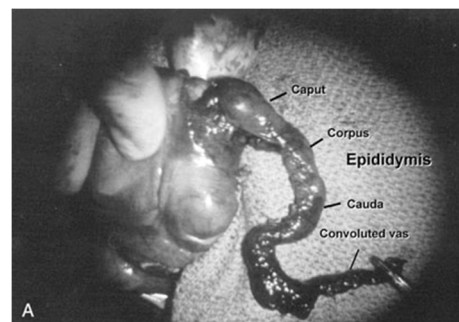


Adapted from Campbell's Urology

Epididymectomy

- After exposure of testis, dissection typically started at convoluted vas, although if large spermatocele, may start in caput
- Because large spermatoceles may distort anatomy, recommend use of micro Doppler to identify testicular vessels
- Epididymal attachments to testis can be individually ligated/cauterized
- Dissection carried as distally as can be easily accomplished

Epididymectomy



Adapted from Campbell's Urology

Complications

- Similar to hydrocele
- Higher risk of recurrence with spermatocelectomy as opposed to epididymectomy
- Damage to vas deferens, epididymis more likely (up to 20%)

Chronic orchalgia

- Defined as scrotal or testicular pain present for at least 3 months without underlying cause
- If underlying cause determined, should be treated appropriately
- Most patients will have tried NSAID's, antibiotics without improvement or resolution
- Frustrating for patient and provider

Evaluation

- Scrotal ultrasound to rule out underlying pathology (low yield)
- Evaluation for other sources of pain
 - Stone
 - Spinal issues
 - Secondary gain
- Trial of medications, including NSAID's, anti-depressants, anti-convulsants
- Minimally invasive procedures, such as spermatic cord block

Surgical treatment-orchalgia

- Vasectomy reversal-rarely indicated
- Microscopic/robotic denervation
 - Should have responded to cord block
 - Can spare vas deferens if fertility still desired
 - Resolution rates up to 75% in selected patients
- Orchiectomy
 - No good evidence of success
 - Last resort
 - Should be via inguinal/subinguinal approach

Key Points of Scrotal Surgery

- Indications for surgery of the epididymis and hydrocele vary, but men of reproductive age should be approached with caution.
- Preoperative imaging with scrotal ultrasonography is almost always indicated.
- Hematoma is the most common complication in scrotal surgery, and extra precautions should be taken to avoid this.

Outline for Seminal Vesicle Topics

- Anatomy
- Conditions seen
 - SV agenesis
 - SV/ejaculatory duct obstruction
 - Hematospermia
 - Malignancy
- Surgery/interventions

SV embryology

- Bilateral dorsolateral bulbous dilations of the distal mesonephric ducts about 12 weeks of gestation
- Vas deferens and ejaculatory ducts also form from mesonephric ducts, join with developing SVs
- Typically fully formed by 7 months gestation
- No female equivalent

SV anatomy

- The arterial supply from the vesiculodeferential artery, branching off from the umbilical artery
- Venous drainage follows the arterial supply draining through the vesiculodeferential veins and the inferior vesicle plexus
- Innervation by the hypogastric nerve (adrenergic and cholinergic) and the pelvic nerve
- Lymphatic drainage through the internal iliac nodes

SV physiology

- Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate
- The pH of the fluid is neutral to slightly alkaline
- The fluid contains fructose and other carbohydrates necessary for sperm motility
- It also contains a coagulation factor and prostaglandins A, B, E, and F

SV conditions

- SV agenesis
- SV/ejaculatory duct (ED) obstruction
- Hematospermia
- Malignancy

SV agenesis

- Bilateral associated with CBAVD, CF
- Unilateral often associated with ipsilateral renal agenesis/anomaly
- Important to identify associated disorders

Bilateral SV agenesis

- Typically associated with CBAVD
- Patient usually present with infertility
- Most often due to mutation of CFTR and/or 5T allele
- Genital form of CF, requires genetic counseling
- Actual involution of vasa, SV during fetal development
- No surgical treatment possible

Unilateral SV agenesis

- Not uncommon, incidence 0.6-1.0%
- May be diagnosed during evaluation for infertility or in case of unilateral vasal agenesis
- Often associated with ipsilateral renal agenesis
- Defect due to mesonephric duct problem early (6-8th week of gestation), leading to agenesis of genital ducts and ipsilateral kidney
- Thus, if patient negative for CFTR/5T mutation, renal U/S indicated
- Although not surgically correctable, important to know

Surgery of the SV

- Several operative approaches have been described
- These include transvesical, transcoccygeal, transperineal, paravesical, and retrovesical
- These are for historical interest only, as nearly all “open” surgery on the SV are now done utilizing minimally invasive techniques
- Endoscopic and transrectal procedures continue to be the most common

SV/ejaculatory duct obstruction

- May be due to trauma, infection, cysts
- Can be total or partial, although partial difficult to assess
- TRUS best test for diagnosis
- MRI reserved for equivocal cases, suspected solid lesions
- Treatment typically only necessary if suspicious for malignancy, symptomatic or infertility present

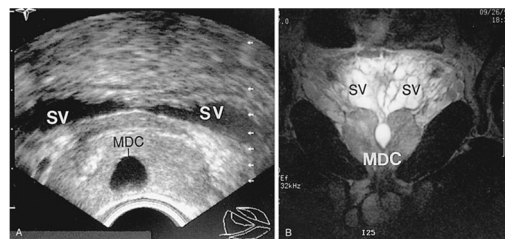
TRUS-guided aspiration

- Used for drainage of symptomatic SV cysts
- Can be sclerosed if recurrent
- Can also be treated endoscopically using TUR or Collins knife (if close to prostate)

TUR-ED

- Indications very specific, include infertility and ejaculatory pain (rare)
- Risks and side effects significant, must be outweighed by potential benefit
- In patients with non-azoospermic infertility (ie, partial EDO), consider sperm banking

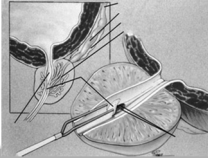
Surgery of the SV



Adapted from Campbell's Urology

TUR-ED

- Resectoscope with small loop used
- Try to minimize cautery, use pure cutting
- Goal is to unroof cyst or obstruction, not remove prostate
- Typically leave catheter until urine is clear



Adapted from Campbell's Urology

Hematospermia

- Typically benign condition
- May be due to inflammation with/without infection, trauma, mass
- Usually self-limiting, may be persistent
- If persistent, TRUS recommended to assess SV, ED, prostate
- Treatment typically NSAID's, supportive care

SV masses

- Cysts
- Benign tumors
 - Cystadenoma
 - Amyloid
- Malignant tumors
 - Adenocarcinoma
 - Sarcoma
 - metastatic

Malignancy

- Most malignancies of SV are metastatic; primary SV tumors are rare
- Often present late in clinical course
- Imaging should start with TRUS (with biopsy), endorectal MRI
- Minimally invasive techniques best option for treatment

Key Points for SV Surgery

- Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate.
- Normal seminal vesicles are not palpable on digital rectal examination.
- Unilateral seminal vesicle agenesis may be associated with ipsilateral renal anomalies and unilateral absence of the vas deferens.
- If there is a palpable seminal vesicle abnormality, TRUS should be performed with biopsy if there is suspicion for malignancy.
- Benign and malignant tumors of the seminal vesicles are very rare.

Conclusions

- Scrotal disorders one of the most common conditions seen in urology
- Various presentations, ultrasound mainstay for diagnosis
- Meticulous surgical technique will prevent most complications
- Most SV disorders benign, can be diagnosed with TRUS
- Occasional need for MRI, other imaging modalities

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21. Figures reprinted from Campbell-Walsh Urology, 9th edition, Sandlow JI, Winfield HN, Goldstein M. *Surgery of Scrotum and Seminal Vesicles*, Ch. 34, Copyright 2007, with permission from Elsevier.



Urinary Trauma – Renal and Upper Urinary Tract

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Philadelphia, PA

Disclosure Statement

- **Nothing to Disclose**

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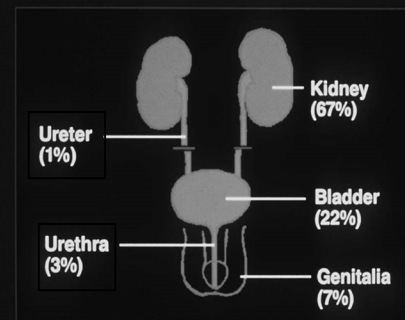
Urotrauma: AUA Guideline

Allen F. Morey, Steve Brandes, Daniel David Dugi III, John H. Armstrong, Benjamin N. Breyer, Joshua A. Broghammer, Bradley A. Erickson, Jeff Holzbeierlein, Steven J. Hudak, Jeffrey H. Pruitt, James T. Reston, Richard A. Santucci, Thomas G. Smith III and Hunter Wessells

From the American Urological Association Education and Research, Inc., Linthicum, Maryland
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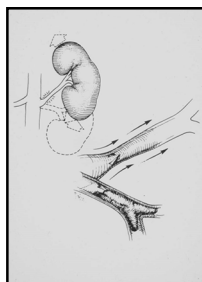
http://dx.doi.org/10.1016/j.juro.2014.05.004
Vol. 192, 327-335, August 2014
Printed in U.S.A.

SITES OF GENITOURINARY TRAUMA



Amount Of Hematuria: Poor Correlation To Severity Of Injury

- **Major lac--GH**
- **Contusion--GH**
- **Renovascular Injury--None***



Mechanism of Injury

- **Blunt Trauma: 80-90%**
 - 125/2320 (5%) **significant***
- **Penetrating Trauma: 10-20%**
 - 178/276 (64%) **significant***
 - **Associated abdominal injuries**

J Urol 1995;154:352

Adult BLUNT Renal Trauma: Who Needs Immediate Imaging?

- **Gross hematuria**

- **MH + Shock**

- >5 RBC/hpf
- SBP<90 mm/

- **“Rapid deceleration” + clinical indicators (rib, vertebral fractures)**



Blunt Trauma: When Can Imaging Safely Be Spared?

- **Isolated microhematuria**

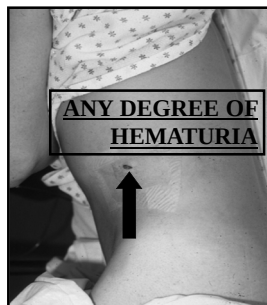
- No shock, symptoms, signs of multisystem trauma

- ****Peds: < 50 RBC/hpf****

- SFGH 25-year experience (n=374)

Buckley et al, J Urol 2004:172

Penetrating Trauma: Higher Index of Suspicion



High Velocity Ballistic Injury



Renal Trauma Staging (CT): Immediate and Delayed Phases

2 Phase Contrast CT

- Vascular (30-45 sec)
- Excretory (5-10 min)

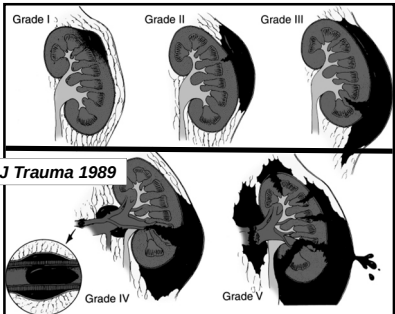


BJU Intl 2004:94

Renal Trauma Imaging: Abd/Pelvic CT with Immediate + Delayed Views

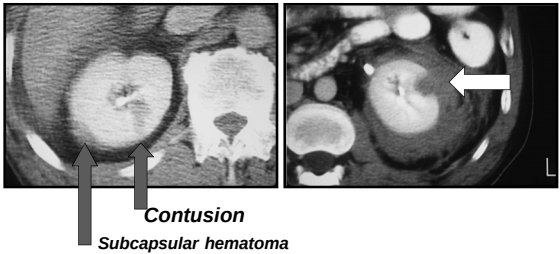


AAST Renal Organ Injury Scale

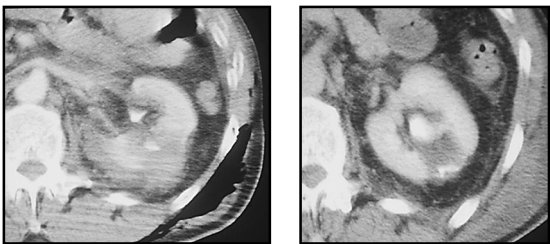


Moore et al, J Trauma 1989

Grade 1 & Grade 2 Injury: Observation



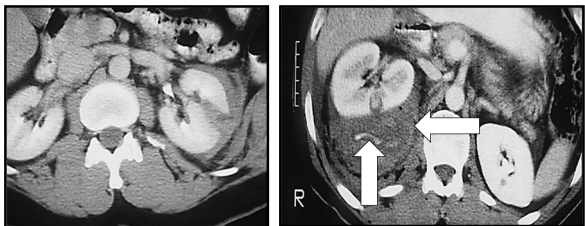
Blunt Grade 3 Injury: Observe



> 1 cm 1 week later

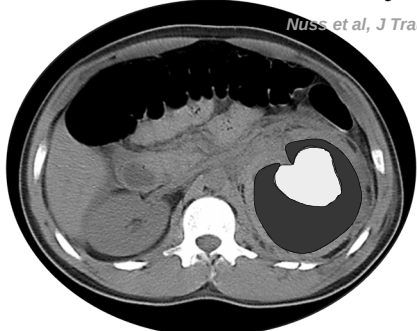
Grade 4 Lacerations More Variable

(And thus more likely "Testable"...)

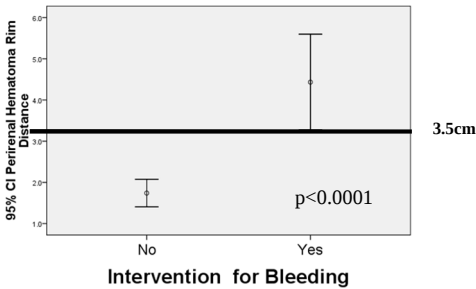


Perirenal Hematoma Size Is Predictive of Need for Intervention After Renal Injury

Nuss et al, J Trauma 2009



Hematoma Size



Intravascular Contrast Extravasation (ICE)



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Urinary Trauma – Renal and Upper Urinary Tract

Trauma/Reconstruction/Diversion

American Association for the Surgery of Trauma Grade 4 Renal Injury Substratification Into Grades 4a (Low Risk) and 4b (High Risk)

Daniel D. Dugli, III, Allen F. Morey, Amit Gupta, Geoffrey R. Nuss, Geraldine L. Sheu and Jeffrey H. Pruitt

From the Departments of Urology and Radiology (JHP), University of Texas Southwestern Medical Center, Dallas, Texas

3 Risk Factors:

1. Perirenal hematoma ≥ 3.5 cm
 2. Complex/medial laceration
 3. Intravascular Contrast Extravasation (ICE)
- Low risk: 0 or 1 risk factor
High risk: ≥ 2 risk factors



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Low Risk vs High Risk

	Low Risk (3/4a)	High Risk (4b)
Intervention (+)	6/84 (7.1%)	12/18 (66.7%)
Odds ratio	1	26.0

$p < 0.0001$

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High Grade Renal Injuries: Application of Parkland Hospital Predictors of Intervention for Renal Hemorrhage

Miranda J. Hardee, William Lowrance, William O. Brant,* Angela P. Presson, Mark H. Stevens and Jeremy B. Myerst

From the Division of Urology, Department of Surgery (M.J.H., W.L., W.O.B., J.B.M.), Center for Reconstructive Urology and Men's Health (M.J.H., W.L., W.O.B., J.B.M.) and Division of Epidemiology (A.P.P.), University of Utah, Salt Lake City and Department of Surgery, Intermountain Medical Center (M.H.S., M.J.H., J.B.M.), Murray, Utah

Risk factors in 115 patients by intervention

	Intervention	No Intervention	p Value
No. pts	8	107	—
Median grade initial hemoglobin (IOR)	12 (10–14)	14 (12–15)	0.23 (Wilcoxon rank sum test)
No. perirenal hematoma (%)	—	—	0.009 (Fisher exact test)
Greater than 3.5 cm	4 (27)	11 (73)	
3.5 cm or Less	4 (40)	96 (90)	
No. laceration (%)	—	—	0.45 (Fisher exact test)
None	1 (7.1)	13 (83)	
Medial	3 (8.6)	32 (91)	
Lateral	0	25 (100)	
Complex/both	4 (9.6)	37 (90)	
No. vascular extravasation (%)	—	—	<0.001 (Fisher exact test)
Yes	6 (27)	16 (73)	
No	2 (2.2)	91 (88)	
No. risk factors (%)	—	—	<0.001 (Cochran-Armitage trend test)
0	1 (3.4)	28 (97)	
1	1 (1.5)	66 (99)	
2	2 (18)	9 (82)	
3	4 (30)	4 (50)	

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Vol. 189, 1771–1776, May 2013
Printed in U.S.A.

Journal of the American College of Surgeons

External Validation of a Substratification of the American Association for the Surgery of Trauma Renal Injury Scale for Grade 4 Injuries

Bradley D. Figler, MD, Bahaa S. Malaeb, MD, Bryan Voelzke, MD, MS, Thomas Smith, MD, Hunter Wessells, MD, FACS

Table 2. Patient Demographics, Stratified by Presence of High-Risk Criteria

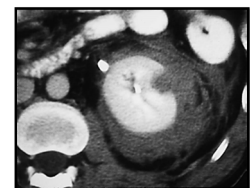
Characteristic	0 or 1 Risk Factors (n = 68)	≥ 2 Risk Factors (n = 19)	All patients (n = 84)	p Value
Mean age, y (SD)	32.1 (8.9)	34.9 (22.4)	32.7 (19.6)	0.63
Sex, n (%)				0.43
Male	41 (62)	13 (72)	54 (66)	
Female	25 (38)	5 (28)	30 (36)	
Mean ISS (SD)	28.2 (17.3)	27.6 (13.1)	28.1 (16.4)	0.88
AAST Grade 4, n (%)				0.001
Laceration	54 (99)	14 (78)	79 (94)	
Hilar injury	1 (2)	4 (22)	5 (6)	
Shattered renal pelvis, n (%)	7 (11)	2 (11)	9 (11)	0.79
Intervention, n (%)	4 (6)	10 (56)	14 (17)	<0.001
Intervention type, n (%)				
Nephrectomy	1 (2)	3 (14)	4 (5)	0.05
Angiography only	2 (3)	2 (11)	4 (5)	0.35
Angiocolectomy	0	5 (28)	5 (6)	<0.001
Mean length of stay, d (SD)	9.4 (12.7)	12.1 (16.3)	10.0 (13.5)	0.52
Readmission, n (%)	2 (3)	3 (17)	5 (6)	0.63
Mean follow-up, mo (SD)	1.9 (3.0)	2.1 (2.4)	2.0 (2.8)	0.76
Renal loss, n (%)	7 (11)	6 (33)	13 (16)	0.31
Death, n (%)	5 (8)	1 (6)	6 (7)	0.27

AAST, American Association for the Surgery of Trauma; ISS, Injury Severity Score.

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Renal Trauma Management

Should use non-invasive management if hemodynamically stable (Standard, Grade B)



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Renal

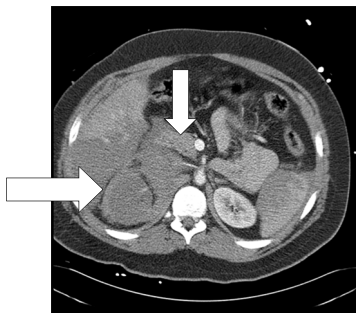
Must perform immediate intervention (surgery or angioembolization in selected situations) in hemodynamically unstable patients with no or transient response to resuscitation. (Standard; Evidence Strength: Grade B)

Damage Control— Consider Nephrectomy

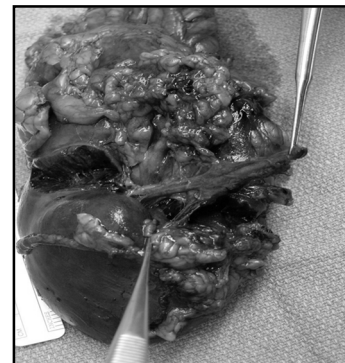


- >3u PRBC transfused?
- Unstable?
- CT: Complex injury? Grade 5?

What Is Your Diagnosis?
(Hint: MVA, Deceleration Injury)



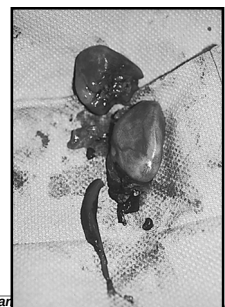
Renal Pedicle Avulsion



Renal Vascular Laceration

- **Vein:** better prognosis than artery
 - Left RV may be ligated if proximal (adrenal, gonadal)
- **Arterial:** usually results in nephrectomy

Shattered Kidney (Grade 5): Nephrectomy Unless Completely Stable



Critical Points for Kidney Trauma

- Know the AAST – Grades dictate treatment
- Stabilize the patient – save nephrons when possible!
- Angiography/Surgery for unstable patients
- Reimage higher grade injuries after 48-72 hrs

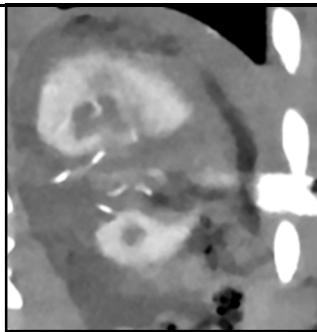
Einstein Urology 2018 @JSimhan Urinary Trauma – Renal and Upper Urinary Tract FOX CHASE CANCER CENTER

Case

- 22M sustained trans-abdominal GSW. Unstable
- Taken to OR emergently for control of bleeding
- R Nephrectomy performed. Pt stabilized in ICU.
- CT A/P obtained

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CT Abdomen/Pelvis



Management?

IR
ANGIOGRAPHY
WITH
EMBOLIZATION

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Trauma/Reconstruction/Diversion

Minimally Invasive Endovascular Techniques to Treat Acute Renal Hemorrhage

Vol. 179, 224S-225S, June 2008

Benjamin N. Breyer, Jack W. McAninch,* Sean P. Elliott and Viraj A. Master
From the Department of Urology, San Francisco General Hospital, University of California-San Francisco, San Francisco, California



- Now more common than renal repair, nephrectomy
- Persistent bleeding from segmental renal vessel
- Transfusion requirement
- AV fistula or pseudoaneurysm
- Not appropriate for main renal artery, vein, pelvis injuries
- Explore if unsuccessful

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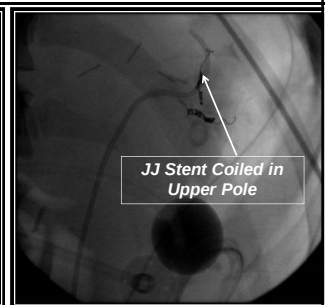
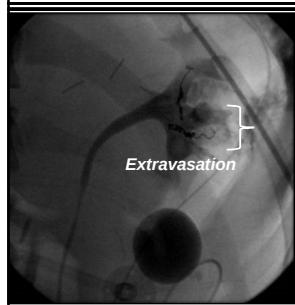
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Case

- Patient was stabilized after IR embolization
 - 2 days after embolization, pt becomes anuric, JP drain starts draining over 2-3 liters/day, Next Step:
- Observation
 - Repeat CT Scan
 - Angiography
 - OR for Nephrectomy
 - Retrograde Pyelogram

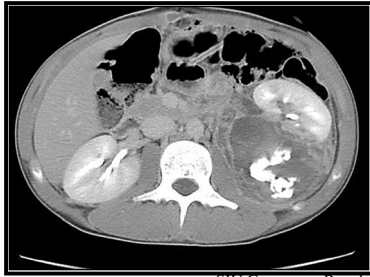
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OR Retrograde



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Grade 4 and 5—Follow Up CT Recommended at 48 Hrs



SIU Consensus Panel, BJU Intl 2004:94

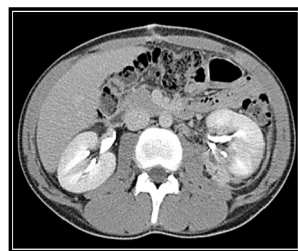
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Renal

Clinicians should perform follow-up CT imaging for renal trauma patients having either (a) deep lacerations (AAST Grade IV-V) or (b) clinical signs of complications (e.g., fever, worsening flank pain, ongoing blood loss, abdominal distention). (Recommendation; Evidence Strength: Grade C)

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Post Embolization: Stent, Foley, Drain



1 Month Later

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Urinary Extravasation: Usually Safely Observed – but needs to resolve!



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Trauma/Reconstruction/Diversion

Nonoperative Management Outcomes of Isolated Urinary Extravasation Following Renal Lacerations Due to External Trauma

Nejd F. Alsikafi,* Jack W. McAninch,† Sean P. Elliott and Maurice Garcia
From the Department of Urology, Mount Sinai Medical Center and University of Chicago Medical Center, Chicago, Illinois, and San Francisco General Hospital and University of California, San Francisco, San Francisco, California
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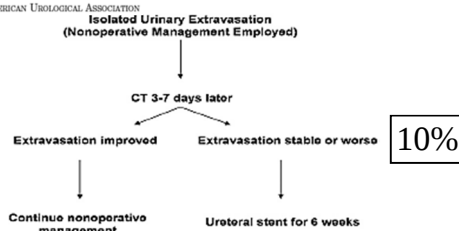


FIG. 1. Management algorithm for isolated urinary extravasation following renal trauma.

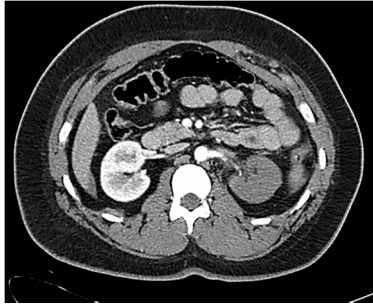
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Urinoma Drainage?

- Clinicians should perform urinary drainage in the presence of complications such as enlarging urinoma, fever, increasing pain, ileus, fistula or infection. (Recommendation; Evidence Strength: Grade C)
- Drainage should be achieved via ureteral stent and may be augmented by percutaneous urinoma drain, percutaneous nephrostomy or both. (Expert Opinion)

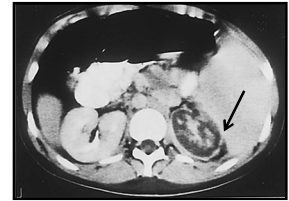
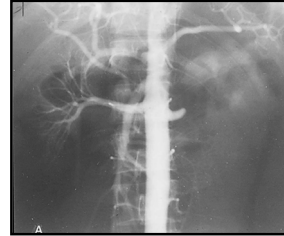
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What Is Your Diagnosis?



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Renal Arterial Thrombosis: Cortical Rim Sign = Delayed Finding



Usually > 8 hours.

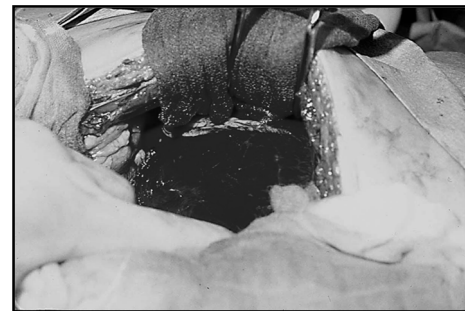
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Renovascular Hypertension?

- **Rare: <1% of 340 renal injuries**
 - Renin secretion
 - Page kidney: decortication
 - AVF (bruit): angioembolization
- **Usually mild—follow/medical Rx**
- **Consider delayed nephrectomy**

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Intraoperative Consult: Retroperitoneal Hematoma?



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Indications for Renal Exploration

- | <u>Absolute</u> | <u>Relative</u> |
|--------------------------------|------------------------------------|
| • Hemodynamic instability | • Non-viable tissue |
| • Expanding pulsatile hematoma | • Persistent Urinary extravasation |
| • Major injury solitary kidney | • Renal artery |
| | • Surgery for associated injury |

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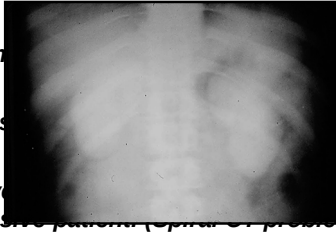
IntraOp One Shot IVP

- Bolus injection of contrast 2cc/kg
- Plain film after 10 minutes
- Confirms presence of contralateral kidney
- May have to wait longer longer for hypotensive patient. (Spiral CT problem)

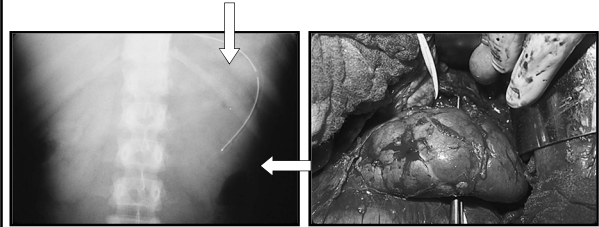
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IntraOp One Shot IVP

- Bolus injection of contrast 2cc/kg
- Plain film
- Confirms
- May have hypotensive patient (spinal cord problem)



Single Shot IVP: Limited Detail



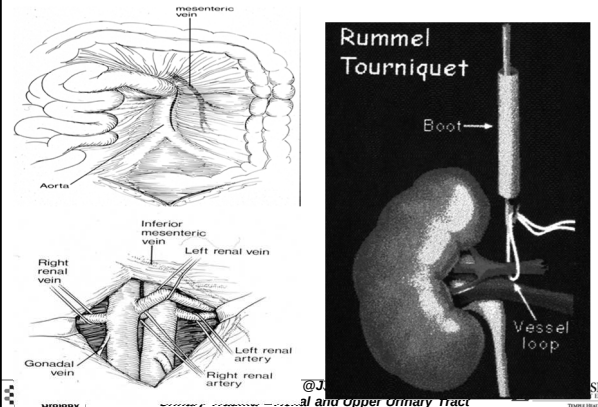
J Urol 1999;161:1088

Why Single Shot IVP?

- Confirms Initial Approach
 - Avoid exploration?
- Contralateral kidney
 - Position?
 - Viability?

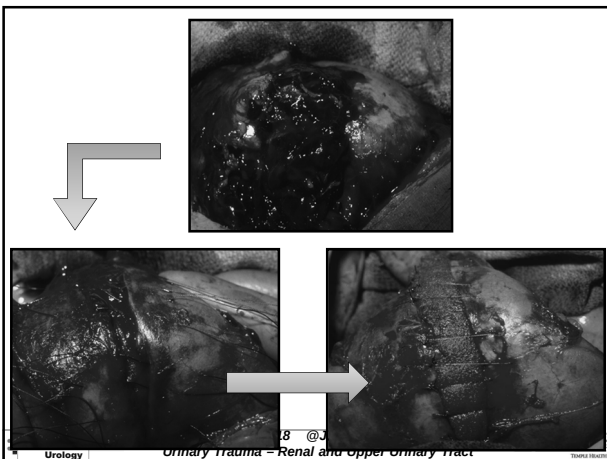


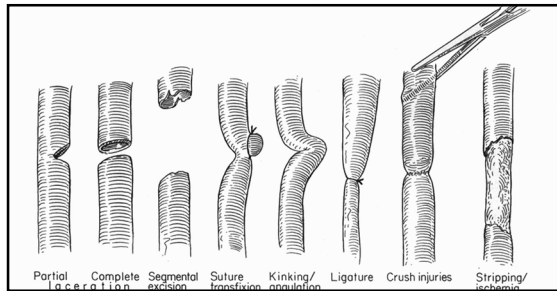
Vascular control



Principles of Renal Reconstruction

- Midline incision
- Early vascular control
- Total renal exposure
- Debridement/hemostasis
- Water-tight closure/ cover defect
- Penrose drain (not suction)





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Ureteral Trauma: Indicators? High Index Of Suspicion

- Hypotension 50%
- Hematuria absent in 25%
- Dx made by 1 shot IVP 7/19 (36%)
- No single test reliably excludes dx

J Urol 2003;170:1213

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Ureteral Trauma: 10 Yr LA County Experience

- Penetrating trauma 95%
- Associated injuries 97%
- Preoperative imaging 12%
- Intraoperative diagnosis 77%

J Urol 2005;173:1202

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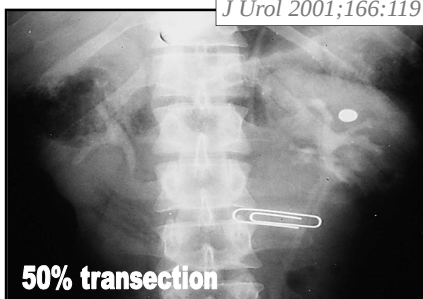
Ureteral Trauma Imaging

Clinicians should perform IV contrast enhanced abdominal/pelvic CT with delayed imaging (urogram) for stable trauma patients with suspected ureteral injuries. (Recommendation; Evidence Strength: Grade C)

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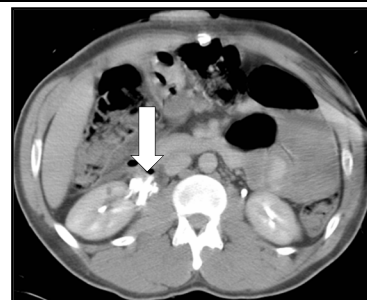
Ureteral Injury Imaging: IVP Rarely Diagnostic (41%)

J Urol 2001;166:119 (Grady)



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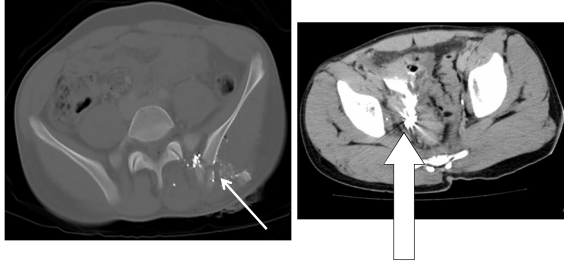
CT More Sensitive Than IVP: Should Include 10 Minute View



J Urol 2003, 170:1213 (SF:GH)

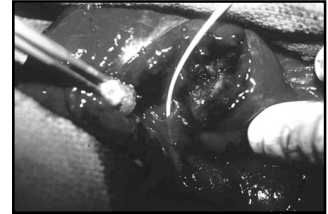
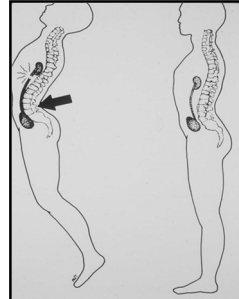
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Ureteral Gunshot Wound: 10 Minute View



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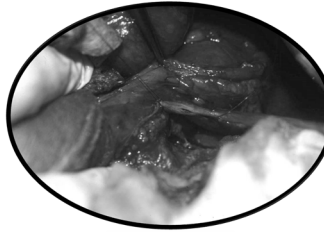
UPJ Disruption – usually in peds and rapid deceleration event



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Ureteral Injury Diagnosis: Surgical Exploration

- Direct inspection
 - Wound location
- Indigo carmine or methylene blue
- RPG sensitive
 - rarely practical in acute setting
 - reserve for delayed



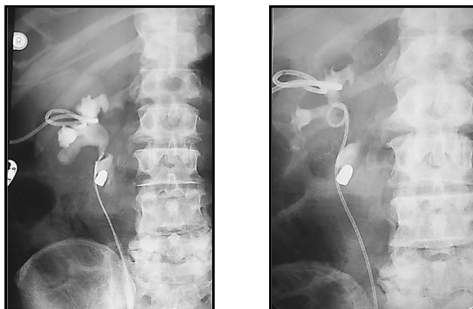
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Ureteral Stent for Traumatic Injury

Surgeons should attempt ureteral stent placement in patients with incomplete ureteral injuries diagnosed postoperatively or in a delayed setting.
(Recommendation; Evidence Strength: Grade C)

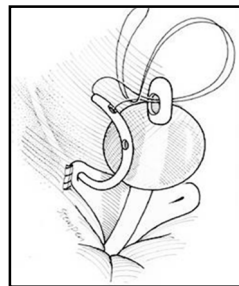
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Endoscopic Management



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Ureteral Contusion



- Stent OK if low-velocity GSW
- Resect and repair if contusion severe

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Iatrogenic Ureteral Injuries

- **Leading cause (~80%)**
- **Gyn > 50% (TAH): distal 1/3**
 - GU, Vasc, Colorectal, Gen Surg
 - Ureteroscopic injuries now uncommon
- **Prior XRT, intraop bleeding, fibrosis, RP mass increase risk**
- **Stent does not assure prevention, may assist in intraop recognition**

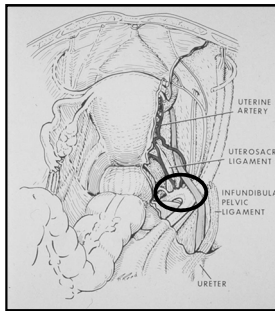
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Timing of Ureteral Repair: When Is Injury Recognized?

- **Intraoperative**
 - Immediate repair preferred
- **< 5 days & stable**
 - Retrograde pyelogram + Stent preferred
 - Immediate repair OK if complex
- **5 or more days—complications more likely**
 - Stent or nephrostomy
 - Drain urinoma
 - Delayed reconstruction

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Urinary Trauma – Renal and Upper Urinary Tract

Ureteral Ligation? Deligate + Stent, Wait 6 Weeks



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Ureteral Fistulae: T or F?

Ureteral fistulae (ureterovaginal and uretero-uterine) often close spontaneously after stent placement alone.

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Ureteral Fistulae: True

Ureteral fistula (ureterovaginal and uretero-uterine) often close spontaneously after stent placement alone.

Br J Urol 1993;65:453

(now in the newly updated AUA Guidelines as well)

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71M--Gross Hematuria

- **Metastatic CaP s/p XRT with subsequent radiation cystitis**
- **Cystectomy with ileal conduit Jan 2013**
- **On ADT currently managed with Sipuleucel T (Provenge)**
- **Known Left uretero-enteric stricture currently managed with indwelling metal ureteral stent (last exchanged early 09/2013)**
- **Transferred from OSH with gross hematuria from conduit**

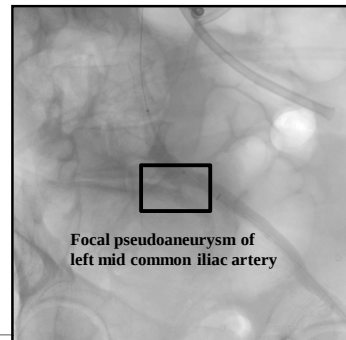
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CT A/P on presentation



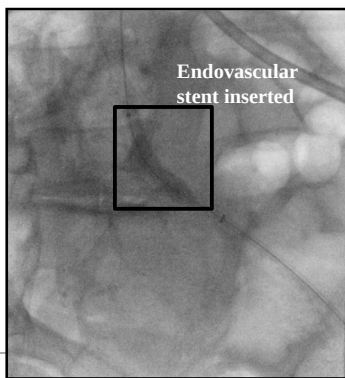
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Left Arteriogram



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Left Arteriogram



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Ureteroarterial Fistula Treatment With Open Surgery Versus Endovascular Management: Long-Term Outcomes

Janelle A. Fox, Amy Krambeck, E. Frederick McPhail and Deborah Lightner*

From the Department of Urology, Mayo Clinic, Rochester, Minnesota

- 20 UAF in 12 year experience (increasing)
- Triad of extensive pelvic surgery, radiation, chronic ureteral stent (hostile abdomen)
- Endovascular stent successful in 85%, preferred
- Lower extremity complications 50%
- Mortality 10%

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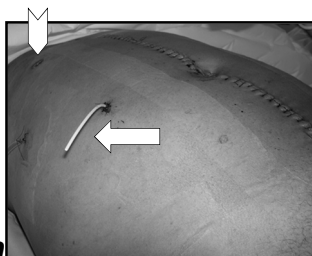
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Vol. 185, 945-950, March 2011

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Urinary Trauma – Renal and Upper Urinary Tract

Ureteral Injury: Damage Control

- Single J stent diversion (distal suture)
- Ligation + PCN, delayed reconstruction



J Urol 2005;173:1202-1205

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PCN for Ureteral Injury

Surgeons should perform percutaneous nephrostomy with delayed repair as needed in patients when stent placement is unsuccessful or not possible. (Recommendation; Evidence Strength: Grade C)

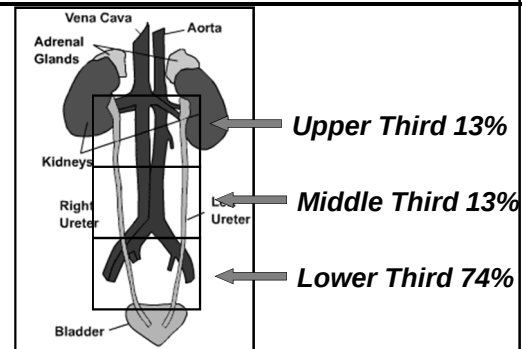
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Principles of Ureteral Repair

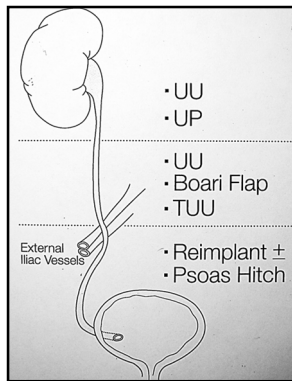
- Debride non-viable tissue
- Wide spatulation
- Tension-free
- Watertight closure
- Stent
- Peri-ureteral drainage (+/-)

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Urinary Trauma – Renal and Upper Urinary Tract

Involved Ureteral Segments



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Repair Type by Injury Location

TUU usually a exam distractor;
Not the answer

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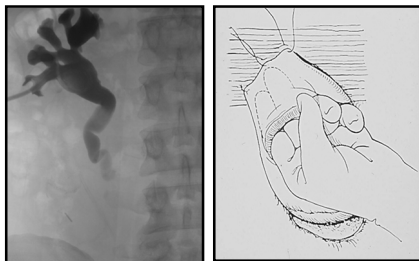
The Different Types of Repairs

- End-to-end over stent
- Reimplant
- Psoas Hitch
- Boari Flap
- TUU
- Bowel interposition
- Auto transplant
- Delayed diagnosis?



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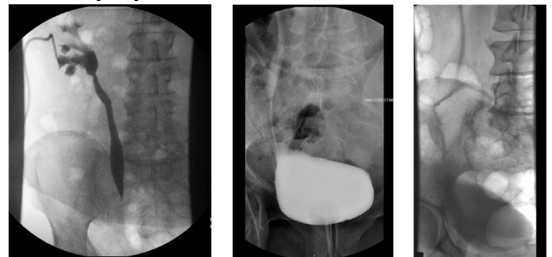
Ureteral Reconstruction Cases



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Psoas Hitch

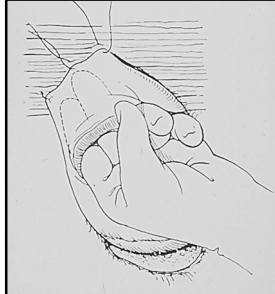
58y/o male, history of right mid-distal stricture after history of multiple stone related endoscopic procedures



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Psoas Hitch Ureteroneocystostomy

- **Highly reliable: 85+% long-term success**
- **Iatrogenic, traumatic inj**
- **Caution**
 - Genitofemoral nerve
 - Femoral nerve (deep)



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Pearls of Psoas Hitch Reimplant

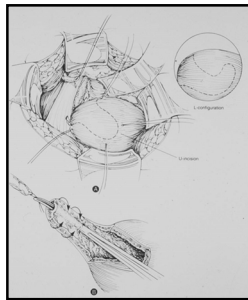
- Mobilize contralateral superior bladder
- Hitch bladder prior to reimplantation-- straight ureteral tunnel with 2 to 4 sutures (absorbable)
- Refluxing, spatulated anastomosis, stent

Marshall, J Urol 1997;158:2078

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Boari Flap Reimplant

- **Lower 2/3 (L4-5)**
- **May compromise bladder volume**
- **Tubularization difficult if detrusor hypertrophied**
- **Not too narrow (flap necrosis)**
- **Planned, delayed repair best**



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How High Can a Boari Go?



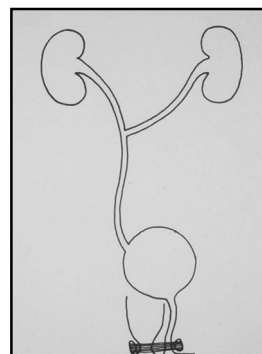
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Delayed Ureteroureterostomy with Downward Nephropexy



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Transureteroureterostomy



- 96% effective in 25 yr Mayo experience (n=63)
- Complications higher for malignant (47%) vs benign (11%), p=0.04
- Above IMA
- End-to-side over stent
- Yo-yo effect → hydro

Iwaszko MR et al. J Urol 2010;183

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Transuretersoureterostomy

Indications:

- **Planned, Delayed**
- **Bladder small, fibrotic, pelvic abscess**
- **Extensive lower ureteral defect**

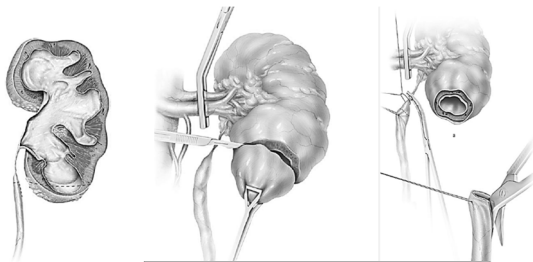
Contraindications:

- **Pelvic radiation**
- **Reflux**
- **Stone disease**
- **Cancer, TB, RPF**

30F with a History of Failed Robotic Pyeloplasty x2



Ureterocalycostomy



Buzz word: "Cortical thinning"

42y/o female. Remote h/o TB. Solitary kidney.



Ileal Ureter → Extensive Defects

- **80+% successful**
- **Contraindicated if renal compromise**
- **Risks: infection, mucus, fistula, stone**
- **Consider: autotransplant, nephrectomy, appendix**



Questions?



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COMPREHENSIVE REVIEW OF UROLOGY BLADDER AND PROSTATE TRAUMA

Richard A. Santucci, MD FACS HON FC Urol(SA)

► Nothing to Disclose

DISCLOSURE STATEMENT

Bladder: Grade

• AAST Organ Injury Severity Scale

I	Hematoma	Contusion or intramural hematoma
	Laceration	Partial thickness laceration
II	Laceration	Extraperitoneal, less than 2 cm
III	Laceration	Extraperitoneal, greater than 2 cm
		Intraperitoneal, less than 2 cm
IV	Laceration	Intraperitoneal greater than 2 cm
V	Laceration	Intraperitoneal or extraperitoneal, extending to 3
		bladder neck or ureteral orifice

Santucci 2018

Bladder: BLUNT: Overview

- **Rare: <2% of all injuries requiring surgery**
- **Often with a severe associated injuries**
- **Often high-energy injuries**
- **Associated with urethral rupture 10-29% and pelvic fracture 6-10%**

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Bladder: PENETRATING: Overview

- **Civilian incidence 2%**
- **Associated major abdominal injuries (35%) and shock (22%)**
- **Mortality high: 12%**

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Bladder: Diagnosis: Physical Signs

- **Suspicion: required in cases of penetrating trauma (no time for studies): trajectory.**
- **Physical signs:**
 - Abdominal pain
 - Abdominal tenderness
 - Abdominal bruising
 - Urethral catheter does not return urine
 - Delayed?
 - Fever
 - No voiding
 - Peritoneal signs
 - ↑ BUN

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Bladder: Diagnosis: Hematuria

- Most (95%) have gross hematuria
- Microhematuria does occur: usually with minimal injury

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Bladder: Diagnosis: Plain Cystography



- Nearly 100% accurate when done properly:
 - Adequate filling with 350 cc or stop with pain
 - Drainage films
- Use 30% contrast
- Underfilling (250 cc) associated with false negatives

8

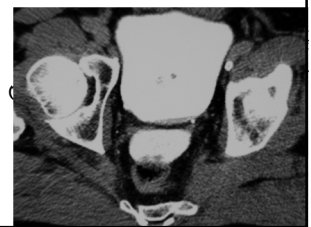
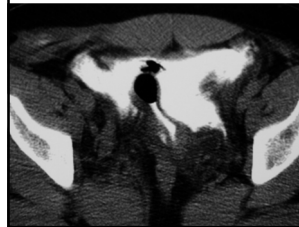
Bladder: Diagnosis: CT Cystography

- Preferred, especially if already getting other CTs
- Anterograde filling by “clamping the Foley” is not OK!
- Must dilute contrast (6:1 with saline, or to about 2-4%)
- Expect 1 in 10 to be positive

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- Extraperitoneal
- Intraperitoneal



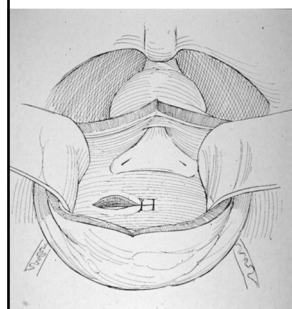
Bladder: Extraperitoneal Rupture

- Alone in 62% of cases
- Combination with intraperitoneal 12%
- Treat “nonoperatively” but watch out for 26% complication rate.
 - Bone fragment in bladder
 - Open pelvic fracture
 - Rectal perforation
 - Poor drainage secondary to bleeding/clots
 - Undergoing laparotomy anyway
 - Undergoing pelvic ORIF anyway
 - Fewer complications (early 5 vs 12%, late 5 vs 21%)

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Bladder: Extraperitoneal Rupture: Repair



- Open bladder and inspect from the inside out
- Check for associated urethral, bladder neck, prostate and rectal injuries
- Repair in 1 layer from the inside
- Drain
- +/- suprapubic tube

12

Bladder: Intraperitoneal Rupture: Repair

- Repair in 2 layers
- ?able advantage to suprapubic tube



Bladder Rupture: Complications

- Foley can be removed in 85% by 10 days
- Generally rare complications
- Acute, self limited urinary frequency is common (gone by 2 months)
- Persistent urinary frequency in 2%

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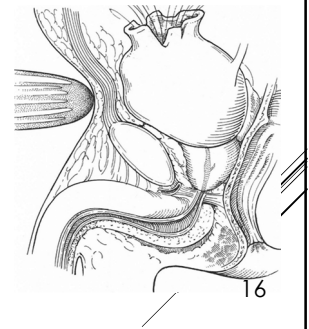
- Review of what the AUA guidelines say on the subject

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BLADDER TRAUMA DIAGNOSIS (14)

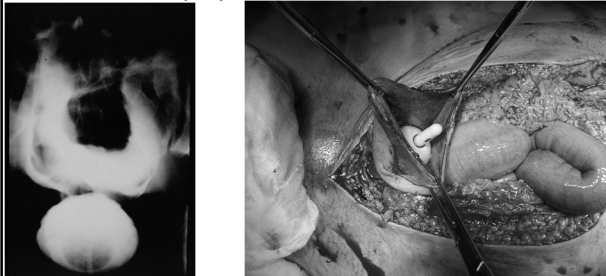
- Patient with gross hematuria and pelvic fracture require cystogram
- Patients with gross hematuria and "mechanism concerning for bladder injury" need cystogram
 - Seatbelt injury mark across low abdomen



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INTRAPERITONEAL BLADDER RUPTURE TREATMENT (15)



- Repair them (open, robotic, laparoscopic)
- Average size = 6 cm

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UNCOMPLICATED EXTRAPERITONEAL BLADDER RUPTURE TREATMENT (16)



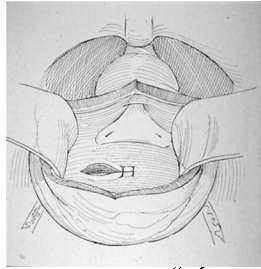
- Drain with Foley
 - If the Foley clots off that's no good
 - NEVER use Continuous Bladder Irrigation (CBI)
 - Never
 - ever

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COMPLICATED EXTRAPERITONEAL BLADDER RUPTURE 17

- ▶ Do laparotomy, repair
- ▶ Definition
 - ▶ Pelvic fracture shards in bladder (these never heal)
 - ▶ Concurrent rectal or vaginal lacerations (head off fistula)
 - ▶ Bladder neck injuries especially in children (not to save continence: to decrease risk of severe sepsis)
 - ▶ Having ORIF pelvis by ortho anyway (keeping urine off their hardware)
 - ▶ Having laparotomy anyway (often they fistulize to laparotomy wound)



19

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ANY BLADDER REPAIR: SUPRAPUBIC TUBES NOT STRICTLY NECESSARY 18

- ▶ No need to put in suprapubic tube in most patients with intraperitoneal or extraperitoneal open repairs
 - ▶ My Caveat: place SPT in all really complex patients (shotgun to bladder)

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20

IATROGENIC BLADDER INJURIES RISK FACTORS [LEVEL 3,4]

- ▶ **Reduced exposure or visibility**
 - Large pelvic masses
 - Pregnant Uterus
 - Obesity
 - Pelvic Hemorrhage
 - Malignant disease
 - Inadequate incision, retraction and/or lighting

21

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IATROGENIC BLADDER INJURIES RISK FACTORS [LEVEL 3,4]

▶ **Anatomy Distortion**

- Adhesions/previous pelvic surgery
- Pelvic organ prolapse
- Congenital anomalies
- Radiation therapy
- Chronic inflammatory pelvic disease
- Endometriosis
- Malignant infiltration
- Distended/thin bladder

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IATROGENIC BLADDER INJURIES

Most frequently injured organ during pelvic surgery
[level of evidence 3]

▶ Frequency	(per 1000 proced.)
• Vaginal Delivery	0.1
• C Section	1.8
• Gynecological Surgery (open)	1.5
• Vaginal Hysterectomy	9
• Radical Cancer Hysterectomy	14
• Obstetric Hysterectomy	61
• Gynecological Surgery (Laparoscopic)	3
• Lap. Assist. Vaginal Hyst.	28

23

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IATROGENIC BLADDER INJURIES FREQUENCY, CONTINUED....

▶ Frequency	(per 1000 proced.)
• TURBT (intraperitoneal)	25
• Bladder neck suspension	9
• Inguinal herniorrhaphy (all)	1.5

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IATROGENIC BLADDER INJURIES

- ▶ Should be identified and repaired immediately
- ▶ Constant surgeon's suspicion and awareness is crucial
- ▶ Laparoscopic surgery entails a risk 2 to 10-fold larger than standard open procedures

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IATROGENIC BLADDER INJURIES ACUTE PRESENTATION

- * Clear fluid in the operative field
- * Visible bladder laceration
- * Gas distension of the urine bag (laparoscopy)

Confirmatory procedures in the OR

- Direct inspection of the bladder walls
- Intravesical instillation of diluted Methylene blue or irrigation fluid through Foley catheter
- Cystoscopy
- Intentional cystotomy to inspect!

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IATROGENIC BLADDER INJURIES ACUTE PRESENTATION

► PRINCIPLES OF REPAIR

- * Same as bladder injuries from external trauma
- * Injuries at laparoscopy can be repaired laparoscopically if: [level of evidence 4,5]
 - Small injury
 - Adequate expertise
 - Adequate view and exposure
 - Ureters or bladder neck not compromised

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27

IATROGENIC BLADDER INJURIES DELAYED PRESENTATION

- * Hematuria
- * Oliguria
- * Elevation of BUN/Creatinine ratio
- * Lower abdominal pain and distension
- * Peritonitis/Sepsis
- * Fistula

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BLADDER QUESTIONS

A 43-year old woman sustains a single gunshot wound to the abdomen. You are consulted at the time of emergency laparotomy for an obvious bullet hole in the dome of the bladder. You should:

- a. open the bladder anteriorly and inspect the inside of the bladder
- b. perform an intraoperative cystogram
- c. debride the bullet hole and close it in two layers
- d. perform an intraoperative IVP
- e. place a ureteral stent

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29

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- d. perform an intraoperative IVP
- e. place a ureteral stent

A: Inspect that bladder! (note that a bullet that made one hole in dome is likely to make a second hole elsewhere as it passes through)

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Following an automobile accident, a 30-year-old comatose man has a blood pressure of 110/70mmHg, plus of 80/min, CVP of 12 cm H₂O and a urinary output of 40ml/hour. There is gross blood in the urine. Nasotracheal intubation has been performed. The first x-ray obtained should be:

- A. Skull
- B. Cervical spine**
- C. Chest
- D. IVP
- E. Cystogram

BLADDER

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31

Following an automobile accident, a 30-year-old comatose man has a blood pressure of 110/70mmHg, plus of 80/min, CVP of 12 cm H₂O and a urinary output of 40ml/hour. There is gross blood in the urine. Nasotracheal intubation has been performed. The first x-ray obtained should be:

- A. Skull
- B. Cervical spine**
- C. Chest
- D. IVP
- E. Cystogram

b. Cervical spine (don't forget your ABC's in trauma)

BLADDER

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32

The most definitive study to rule out traumatic bladder rupture is:

- A. Pelvic CT scan
- B. Cystoscopy
- C. Pelvic ultrasound
- D. CT cystogram
- E. IVP

BLADDER

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33

The most definitive study to rule out traumatic bladder rupture is:

- A. Pelvic CT scan
- B. Cystoscopy
- C. Pelvic ultrasound
- D. CT cystogram**
- E. IVP

D: CT cystogram (or plain cystogram but not offered)

BLADDER

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34

A 26-year-old woman has a pelvic fracture, collapsed lung and a severe closed head injury following an automobile accident. A retrograde cystogram reveals an extraperitoneal bladder rupture. The next step in management is:

- ▶ A. Catheter drainage
- ▶ B. Immediate surgical repair
- ▶ C. Diagnostic peritoneal lavage
- ▶ D. Abdominal and pelvic CT scan
- ▶ E. Suprapubic cystostomy

BLADDER

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35

A 26-year-old woman has a pelvic fracture, collapsed lung and a severe closed head injury following an automobile accident. A retrograde cystogram reveals an extraperitoneal bladder rupture. The next step in management is:

- ▶ **A. Catheter drainage**
- ▶ B. Immediate surgical repair
- ▶ C. Diagnostic peritoneal lavage
- ▶ D. Abdominal and pelvic CT scan
- ▶ E. Suprapubic cystostomy

A: catheter drainage

BLADDER

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36

A 42-year-old man is undergoing laparotomy for intra abdominal injuries and bladder rupture. Bleeding is noted in the perivesical area. After repair of bladder rupture, pelvic pressure does not stop the persistent oozing. Multiple blood transfusions are given and his core temperature is 35.5 degrees Celsius. The next step is:

- ▶ A. Intraoperative arteriography
- ▶ B. Ligation of the hypogastric arteries
- ▶ C. Intravenous aminocaproic acid
- ▶ D. Close the abdomen and place patient in a MAST suit
- ▶ E. Pack pelvis and close abdomen

BLADDER

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37

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- ▶ C. Intravenous aminocaproic acid
- ▶ D. Close the abdomen and place patient in a MAST suit
- ▶ **E. Pack pelvis and close abdomen**

E: pack pelvis (damage control!)

BLADDER

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38

Urethral Trauma

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Disclosures

- Industry or pharmaceutical support: None
- Male urethral injury management: None

Objectives

- Review epidemiology, etiology, evaluation, management, and complications of urethral trauma
- Classification
 - Traumatic
 - Evaluation
 - Management
 - Iatrogenic
 - Etiology
 - Management
 - Impact
 - Artificial Urinary Sphincter (AUS) Erosion
 - Incidence
 - Management

Introduction – Urethral Trauma

- The urethra is not commonly injured from external violence and only accounts for 4% of all genitourinary trauma
 - Majority of urethral injuries are the result of blunt force trauma
- Anatomic categorization of injury: urethra divided into the anterior and posterior segments at the level of the genitourinary diaphragm
- Due to anatomic position, each segment has very different sources of injury and initial treatment options
- Most urethral injuries occur in men due to the longer urethral length and higher incidence of traumatic injuries in men

Definitions

- Trauma
 - Refers to injury caused by external force from a variety of mechanisms, including traffic- or transportation-related injuries, falls, assault (e.g., blunt weapon, stabbing, gunshot), explosions, etc.
- Injuries
 - Are the results of trauma and the force imparted on the particular body part of organ.
 - Typically categorized as blunt or penetrating based on mechanism
 - Blast injuries are unique and have components of both blunt and penetrating mechanism

Definition – Urethral Trauma

- Urethral injuries are dependent on the anatomic location (anterior versus posterior)
- The impact, complications, and management of urethral injuries are highly variable and greatly dependent on the mechanism, involvement of surrounding structures, and severity
 - **Blunt injuries:** Contusion, laceration, and avulsions
 - **Penetrating injuries:** Laceration, transection, and blast injury with delayed stenosis
 - **Iatrogenic:** Result from endoscopic injuries and instrumentation
 - Range from minor mucosal abrasions, to lacerations and penetrations, and thermal injury

Epidemiology

- Incidence of trauma is rising
- WHO estimates that by 2020 road traffic injuries will be the 6th leading cause of death
- Renal trauma occurs in 1-5% of all trauma cases (Santucci, Wessells et al. 2004)
 - The kidney is the most commonly injured genitourinary organ
 - Incidence of renal injury of 4.89 per 100,000 persons (Wessells, Suh et al. 2003)
 - Recent NTDB reports estimate solid abdominal organ injuries occur in approximately 7% of total injuries (Hurtuk, Reed et al. 2006)
 - Based on current US population data 15000 persons will sustain renal injury annually

Epidemiology

- Pelvic injuries occur in 5% of all injuries in the United States
- Urethral and bladder injuries occur in 10-15% of pelvic fractures (Bariol, Stewart et al. 2005), (Paparel, N'Diaye et al. 2006)
 - Recent estimate of the incidence of pelvic fracture injury was greater than 31,000 over a five year period (Bjurlin, Fantus et al. 2009)
 - Based on that current population, > 6000 urethra and bladder injuries occur in the same time period
 - Urethral injuries are often associated with specific fracture patterns
 - (Basta, Blackmore et al. 2007)

Epidemiology - Iatrogenic Urethral Trauma

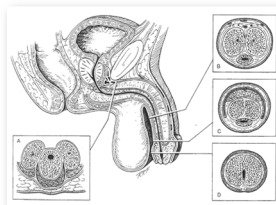
- Incidence of urethral catheterization
 - No exact incidence or number of inpatients catheterized
 - 24 million catheters are purchased by hospitals each year (Saint et al. 2000)
 - Estimates outside the US are 10-25% of hospitalized patients (Jain et al., 1995)
 - One study noted 11000 catheter placements per year (Davis et al., 2016)
- Incidence of urethral injury
 - 0.3-3% of hospitalized patients incur iatrogenic injury (Bhatt et al 2015)
 - 0.7-6.7 per 1000 male urethral catheterizations (Kashefi et al 2008, Davis et al 2016)
- Impact on urology consultations
 - 6% of urology consultations (864 total) (Thomas et al. 2009)
 - 32.9% of urethral injuries over a five year period (Dobrowolski et al., 2002)

Anatomy – Urethral Trauma

- The male urethra is anatomically divided into two areas referred to as the anterior and posterior urethra
 - The genitourinary diaphragm is the point of anatomic differentiation
- Components of the anterior urethra - distal to proximal
 - Fossa navicularis
 - Penile or pendulous
 - Penile urethra and fossa navicularis comprise slightly more than half of the distal anterior urethra
 - External to the body in the penis
 - Bulbar segments
- Posterior urethra is composed of two segments
 - Membranous
 - Prostatic
 - Both intimately related to the bony pelvis and are injured more frequently in pelvic fractures

Anatomy – Urethral Trauma

- Urethral Anatomy (Gross)

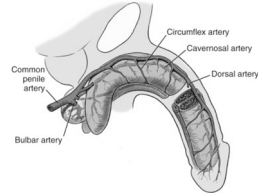


Anatomy – Urethral Trauma

- Blood supply to the urethra arises proximally from the internal pudendal artery
 - Becomes the common penile artery which terminates into the bulbourethral artery
 - Common penile and bulbourethral arteries are the main blood supply to the urethra
 - These arteries arborize in the glans of the penis and retrograde perfusion of the urethra is maintained when the bulbar arteries are transected
- Small perforating arteries from the inferior aspect corporal bodies then enter the dorsal urethra at their attachment
- The venous outflow of the urethra parallels the arterial supply

Anatomy – Urethral Trauma

• Urethral Blood Supply



Etiology – Urethral Trauma

- **Blunt**
 - Majority of urethral injuries are the result of blunt force trauma
 - **Anterior urethra**
 - Bulbar anterior urethral segment is the most commonly injured segment
 - Accounts for 85% of anterior urethral injuries
 - Typically the result of a straddle type fall or direct blow to the perineum and are usually lacerations
 - The penile bulb urethra can be injured in association with pelvic fracture if force tearing the corporal body damages the corpus spongiosum as well
 - **Posterior urethra**
 - Almost uniformly associated with pelvic fracture
 - Approximately 5-4% of male and female patients with pelvic fracture have associated posterior urethral injuries
 - Result of stretching and tearing forces at the level of the membranous urethra resulting in laceration or rupture
 - Patients that sustain a urethral injury after blunt pelvic fracture are often severely traumatized suffering multi-system trauma and have high injury severity scores
- **Penetrating**
 - Result of gunshot wounds or stab wounds
 - 3% of gunshot wounds to the genitourinary system involve the anterior urethra
 - 40-50% of patients with penetrating wounds to the penis have concomitant injuries to the urethra
 - Penetrating posterior urethral injuries have similar mechanism to anterior although impalement injuries occur in this area
 - Associated with injuries to surrounding structures such as rectum and pelvic vasculature
- **Iatrogenic**
 - Result of urethral catheter placement
 - Analysis have shown an incidence of 3.2 per 1000 patients
 - Male posterior urethral injuries are more often related to instrumentation of the urethra primarily endoscopic surgical procedures

Etiology - Iatrogenic Urethral Trauma (AUS)

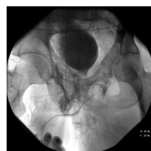
- **Erosion Rates**
 - Contemporary series 5-10% (Lai et al, 2007)
 - Recent high risk series reported rate of 6.2% (Brandt et al, 2016)
 - Some discrepancy due to concomitant infections
- **Etiology**
 - Early erosion due to iatrogenic urethral injury
 - Late erosion due to other iatrogenic factors, e.g. catheter placement
 - Subset of spontaneous erosions

Presentation – Urethral Trauma

- Based on the anatomic differences of the male and female urethra - urethral injuries have a variable presentation
- **Anterior:**
 - Most of these injuries are located in the mid-perineum, where the urethra is crushed against the pubic arch
 - Penetrating injuries present with obvious wounds to the perineum or penis.
- **Posterior:**
 - Present in the context of severe multisystem trauma
 - The initial steps in evaluation include the ABCs - airway, breathing, and circulation
 - Although patients cannot be directly interviewed, information concerning mechanism of injury, blunt versus penetrating, and details of that mechanism, i.e. high speed motor vehicle collision or high velocity missile injury, should be obtained
 - Physical examination of these patients is difficult, especially in blunt trauma, as posterior urethral injuries are highly associated with pelvic fracture and up to 15% of these have associated bladder injury
 - Patients with the combination of blood at the urethral meatus, inability to void, and pelvic fracture should be presumed to have posterior urethral injury
- **Female:**
 - Female urethral injuries are associated with 0-6% of patients with pelvic fracture
 - Female patients with urethral injury may have hematuria or vaginal lacerations

Presentation – Urethral Trauma

- **Physical Exam Findings**
 - The classic triad of blood at the urethral meatus, inability to void, and palpably distended bladder is uncommon in clinical practice
 - Blood at the urethral meatus is variable in presentation and occurs in 37-93% of patients
 - Patients who present with blood at the urethral meatus, especially in the setting of pelvic trauma, evaluation of the urethra is mandatory
 - Patients with bulbar urethral injuries may present with a perineal hematoma
 - The hematoma is confined by Colles' fascia which is continuous with Scarpa's fascia and contiguous with the dartos fascial layers
 - The hematoma can have a classic appearance of a butterfly within the perineum, due to rupture of Buck's fascia, and can spread into the scrotum or up the abdomen along the layers of Dartos and Scarpa's fascia
 - Patients with posterior urethral injuries may have a "high-riding" or ballotable prostate on exam



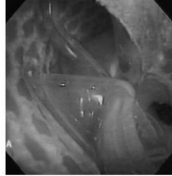
- Inability to pass a catheter following pelvic trauma can be a hallmark of a serious urethral injury
 - Inadvertently, catheter can be passed into the pelvic hematoma

Presentation – Iatrogenic Urethral Trauma

- **Etiology**
 - Inadvertent inflation of balloon in the urethra
 - Balloon pressures reach > 700 kPa (~ 102 PSI)
 - False passage at the level of the bulbar or penile urethra
- **Diagnostic Criteria**
 - Blood per urethra/Gross hematuria with catheter placement
 - Non-draining catheter
 - Penile/Perineal pain
 - Cystoscopic evidence of urethral injury
 - Contrast extravasation on retrograde urethrogram

Presentation - Iatrogenic Urethral Trauma (AUS)

- Symptoms
 - New onset incontinence
 - Hematuria
 - Urinary tract or genital skin infection
- Evaluation
 - Physical exam
 - Cystoscopy



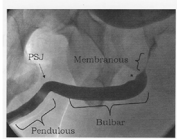
Siegel et al, 2015

Urethral Trauma

- Evaluation – Which patients
 - Guideline statement 19
 - Patients with blood at the urethral meatus after pelvic fracture
 - Blood at meatus
 - 37-93% in posterior urethral injury
 - 75% in anterior urethral injury (Mouraviev, Coburn et al. 2005), (Elgamal 2009)
 - No attempt at catheter placement prior to RUG
- Evaluation – How
 - Retrograde Urethrogram



Evaluation - Urethral Trauma



Normal RUG



Posterior Urethral Injury RUG



Imaging – Urethral Trauma

- When a urethral injury is suspected, a retrograde urethrogram is performed
 - Key aspect is placement of the patient in a 30-45° lateral decubitus position to ensure adequate visualization of the entire urethra
 - Partial injuries to the urethral lumen will reveal some contrast extravasation coupled with passage of a variable amount of contrast into the lumen of the bladder
 - In complete urethral transection, a dramatic bloom of urinary contrast extravasation at either the bulbomembranous junction or the prostatic apex
 - Another key consideration in urethral injury imaging is pattern of pelvic fracture
 - Pelvic fractures that produce urethral injury involve the anterior arch of the pelvis ring
 - Specific fractures that are associated with a greater risk of urethral injury are pubic symphysis diastasis and inferior pubic rami fracture, especially in the medial aspect of the rami
 - In patients with urethral injury accompanied by pelvic fracture, it is essential to evaluate for concomitant bladder injury
 - Combined bladder and urethral injury is found in 10-29% of patients with bladder injury and pelvic fracture



Diagnostic Testing - Urethral Trauma

- Cystoscopy can be used to diagnose urethral injury
 - Patients taken directly to the operating room for hemodynamic unstable or from penetrating trauma cystoscopy is used to inspect the urethra
 - In partial urethral injury, cystoscopy can facilitate Foley catheter placement
- In patients with penetrating injuries to the posterior urethra, rectal injury should be considered
- Female patients with pelvic fracture and physical findings concerning for urethral injury should be evaluated
 - Retrograde urethrogram is not technically feasible for the assessment of the urethra in pelvic trauma
 - Best diagnostic test is cystoscopy
 - Either a flexible cystoscope or special rigid scope without a cutback beak

Management - Urethral Trauma

- Management – Catheter Drainage
 - Guideline statements 20, 21, 25
 - Establish prompt urinary drainage in patients with pelvic fracture associated urethral injury
 - A urologist may attempt a retrograde catheter placement in partial urethral injuries
 - May place suprapubic tubes (SPTs) in patients undergoing open reduction internal fixation (ORIF) for pelvic fracture
 - Establish prompt urinary drainage in patients with straddle injury to the anterior urethra (Rosenstein and Alsikafi 2006)
 - Acceptable options include urethra catheter (if possible) or suprapubic cystostomy tube

Management - Urethral Trauma

- Management – Endoscopic
 - Guideline statement 22
 - Perform primary realignment (PR) in hemodynamically stable patients with pelvic fracture associated urethral injury
 - Not perform prolonged attempts at endoscopic realignment in patients with pelvic fracture associated urethral injury

Management - Urethral Trauma



Management – Urethral Trauma

- Anterior urethra
 - Management varies based on mechanism
 - Blunt urethral injuries - primary objective is urinary diversion
 - Diversion with either urethral Foley catheter placement or suprapubic cystostomy tube placement
 - Penetrating injuries should have immediate operative intervention
 - Low velocity gunshot or stab wound and limited tissue loss, primary surgical repair is indicated
 - Performed using absorbable suture creating a spatulated primary repair
 - High velocity gunshot or significant tissue loss, urinary diversion only is performed

Urethral Trauma

- Management – Surgical
 - Guideline statement 24
 - Perform prompt surgical repair in patients with uncomplicated penetrating trauma of the anterior urethra (Broghammer and Wessells 2008), (Brandes 2006)
 - If feasible primary reconstruction using two layer technique with fine absorbable suture
 - If damage is excessive or significant blast effect, temporary urethrostomy at site of injury
 - Delayed reconstruction of urethral defect

Management – Urethral Trauma

- Posterior urethra
 - Variable location of injuries - distally beyond the external sphincter or at the prostatic apex just proximal to the external
 - Depends the nature and location of the pelvic fracture as well as the ligamentous attachments to the prostate
 - The immediate goal in management of complete urethral disruption is to obtain urinary drainage, usually with the placement of a suprapubic tube
 - Although controversial, patients may also undergo endoscopic realignment of the urethra, 3-10 days after injury, when stable from their pelvic injury
 - Not clear if endoscopic urethral realignment offers any benefit and prolonged efforts at realignment are not recommended
 - Immediate operative repair of posterior urethral injuries is not indicated
 - Posterior urethral injuries are well suited to "damage control" maneuvers and many adjunct and reconstructive procedures are well described options
 - Most experts agree that immediate repair of these injuries can be dangerous and leads to an acceptably high rate of restenosis
 - Exceptions to this are bladder neck injuries or extension of a bladder or bladder neck injury into the anterior portion of the prostatic urethra within the pelvis
- Female urethra
 - Repaired at time of presentation unless the patient is hemodynamically unstable due to association with vaginal lacerations
 - Repair is recommended during the initial hospital course to minimize the chance of post injury urinary incontinence or development of urethrovaginal fistula
 - Distal female urethra may be managed expectantly or marsupialized as the continence mechanism is usually spared

Management - Iatrogenic Urethral Trauma

Intervention	No.	Management
Replacement of catheter by Urology	23	• 3 studies evaluated incidence of injury
Manipulation of catheter by Urology	3	• Range of 2-6.7 per 1000 catheters
Placement of 3-way catheter	3	• All patients required urologic intervention
Cystoscopy with guidewire catheter placement	18	• All patients developed short term complications
Rigid cystoscopy in operating room for catheter	1	• Clavien-Dindo complications ≥ grade 2 occurred in 81% of patients (Davis et al, 2016)
Cystoscopic or percutaneous suprapubic tube	17	• 40% of patients developed urosepsis
Open cystostomy tube	1	• Overall 14 patients
Laparotomy with cystorrhaphy and catheter	1	• ICU admission in 3
Total	67	

Management - Iatrogenic Urethral Injury (AUS)

- Traditional management is placement of Foley catheter
 - Concept is to allow for re-epithelialization of the urethra
 - Many men will develop urethral stricture
 - Secondary urethral healing delays surgery AUS replacement and treatment of incontinence
- Some have advocated primary repair of the urethra at time of explanation (Rozanski et al 2014), (Chertack et al, 2016)
- In theory, urethral re-approximation should allow for closure of defects and mucosal apposition
- Case reports exist of leaving asymptomatic erosions in situ (Singla and Singla, 2015)

Iatrogenic Urethral Injury - Outcomes

- Significant increase in cost and length of stay
 - Total cost \$375,815
 - Current € 1 = \$ 1.12
 - Increased length of stay
 - Range 2.07 – 9.4 ± 10 days
 - Poor documentation to corroborate urethral injury from catheter attempt
- Limited long term clinical data
 - Davis et al 2016
 - 24% Suprapubic catheter
 - 21% Indwelling Foley catheter
 - 24% Perform intermittent cath
 - 11% Required dilation

Table 4. Breakdown of initial financial burden due to iatrogenic urethral injury during UC

	No.	Cost (€)	Total Cost (€)
Inpatient stay in ICU	3 (7.7 nights total)	2,000/Night	48,000
Inpatient stay in ward (total)	34 (220 nights total)	800/Night	272,000
Flexible cystoscopy	13	100	1,300
SPC	12	100	1,200
Surgical drains (open - cystostomy)	1	3,000/Dr	3,000
Access to bladder			
Retropubic urethrostomy	2	250	500
Urethrogram	17	40-50	800
Catheters	37	20-40	1,400
Total cost			385,377

The initial costs are evidence of managing long-term complications with an urethral stricture disease and follow-up subsequent appointments which lead to an even greater cost burden on the department.
Source: Finance departments at St. Vincent's University Hospital and Tallaght Hospital, Dublin, Ireland.

Davis et al, 2016

Iatrogenic Urethral Injury (AUS) – Outcomes

- In situ urethroplasty (Rozanski et al, 2014)
 - Retrospective analysis of 26 patients undergoing explanation of eroded AUS
 - 6 year time frame from single center experience
 - 13 patients received urethroplasty
 - 13 patients treated with catheter alone
 - Technique
 - 2-0 monofilament suture is used to close the urethral defect in a single layer over 14-16 Fr Foley catheter
 - Results
 - Significant reduction in urethral stricture formation
 - 38% (5/13) vs 85% (11/13)
 - No significant increase in operative time
 - 78 vs 70 minutes
 - Trend toward faster secondary procedure

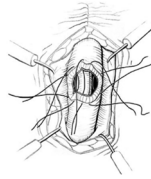


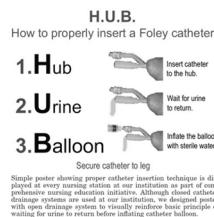
Figure 1. (8x) is performed for reapproximating normal edges of urethra at site of AUS with suture using 2-0 monofilament suture over 14 or 16 Fr Foley catheter while dorsal aspect is left intact.

Iatrogenic Urethral Injury (AUS) – Outcomes

- Abbreviated urethroplasty vs primary urethral anastomosis (Chertack et al, 2016)
 - Retrospective analysis of 75 patients undergoing explanation of eroded AUS
 - 10 year time frame
 - 52 patients received Foley catheter alone
 - 15 patients underwent primary urethral anastomosis
 - 8 patients underwent abbreviated urethroplasty
 - Technique
 - Abbreviated urethroplasty
 - Single layer closure without urethral mobilization
 - Primary urethral anastomosis
 - One and two layer closure of bulbar urethra (4-0 and 5-0 monofilament suture)
 - One layer closure of penobulbar urethra (4-0 monofilament suture)
 - Results
 - Significantly higher urethral stricture rate with severe erosions managed with Foley catheter only
 - Primary anastomosis was used only for severe erosion (> 50% circumference)
 - Higher incidence of stricture formation in Foley catheter only comparing mild (< 50%) and severe (> 50%) erosion
 - Equivalent formation of urethral diverticulum between all groups
 - No difference in number or time to repeat AUS placement

Iatrogenic Urethral Injury – Prevention Strategies

- Education
 - Kashefi et al demonstrated 5 fold decrease with nursing education
 - 1 hour didactic session
 - 2 hour hands on skills lab
 - Educational posters at nursing stations
 - Incidence ↓ from 3.2/1000 to 0.7/1000
- Others have evaluated house staff education at tertiary referral hospitals



Iatrogenic Urethral Injury – Prevention Strategies

- Build a better catheter
 - Human urethra is injured with increase in diameter > 40% of baseline
 - Minimum required pressure:
 - 187 kPa = 27 PSI
 - Different catheter materials transmit pressure differently (Wu et al, 2011)
 - Silicone force > 200 kPa in the urethra
 - Latex catheters > 150 kPa in the urethra
 - Silicone catheter burst with ↑ pressure
 - Syringe with safety valve limits pressure to 150 kPa



Complications - Urethral Trauma

- Monitoring Complications
 - Guideline statement 23
 - Monitor patients for complications (e.g., stricture formation, erectile dysfunction, incontinence) for at least one year following urethral injury
 - Patients are at risk for erectile dysfunction and incontinence
 - Pelvic fracture urethral injury (PFUI) has a low risk of incontinence
 - Pelvic fracture and damage to surrounding structures is typically the cause of erectile dysfunction and/or incontinence
 - Incontinence risk 4-18%
 - Erectile dysfunction risk 24-46% (Mouraviev, Coburn et al. 2005)

Complications – Urethral Trauma

- Urethra
 - Serious long-term sequelae often accompany traumatic urethral injury
 - Most urethral injuries are associated with dense fibrosis in the intervening gap created by transection
 - Urethroplasty is the most appropriate therapy to reestablish patent urethra after traumatic injury
 - Outcomes of posterior urethroplasty are excellent an average rate of approximately 89%
 - Other complications include diverticula formation, urinoma, or fistula to the perineum or rectum

Study	n	Follow-up (years)	Mean Success
Chapman et al. (1987)	14	1-10	85%
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Chapman et al. (1987)	14	1-10	85%

Complications – Urethral Trauma

- Erectile dysfunction
 - Common after pelvic fracture urethral injury
 - Attributed to injury of the parasympathetic nerves as they travel along the lateral border of the prostate
 - Can be purely arteriogenic
 - Results from damage to the internal pudendal artery from trauma or embolization
 - Erectile dysfunction may recover over time, but can take up to 2 years to occur
- Incontinence
 - Rare consequence of urethral injury
 - Bladder neck is typically intact
 - External urinary sphincter is damaged in nearly all cases – as a result of the initial trauma or the urethroplasty
 - With initial concomitant bladder neck or serious pelvic nerve injury incontinence can occur after posterior urethroplasty
 - An incompetent bladder neck can predict this problem pre-operatively

Study	n	Follow-up (years)	Mean Success
Chapman et al. (1987)	14	1-10	85%
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Chapman et al. (1987)	14	1-10	85%

Urethral Injury: Conclusions

- Iatrogenic Foley catheter injuries
 - Result in significant increased cost and patient morbidity
 - Simple education and demonstration of catheterization technique can significantly reduce incidence of injury
 - Better catheter design can reduce severity and incidence of catheter related urethral injuries
- Urethral injury due to AUS erosion
 - Erosion is a less common cause of urethral injury (5-10%)
 - Immediate repair of significant injuries appears to result in lower incidence of complications
 - Simple repair does not increase operative times
- Urethral Trauma
 - Often associated with blunt injury and more common in the proximal urethra
 - Key management point is establishing urinary drainage
 - Patients with urethral injury from all etiologies should be monitored for at least one year for complications related to their injury.



GENITAL TRAUMA

Lee C. Zhao



Disclosures

- None

2 Division Name or Footer



Genital Trauma—Male

	Penetrating	Blunt
Penile	Penile injury	Penile fracture
Scrotum	Scrotal injury	Testicular rupture

3 Division Name or Footer



Penetrating penile injury



4 Division Name or Footer

Penetrating penile injury

- Evaluation: physical exam
- Imaging: retrograde urethrogram if urethral injury suspected
- Surgical exploration
- Mechanism of injury—approach for exploration, antibiotic choice

5 Division Name or Footer



Bites

- Antibiotics
- Vaccination
- HIV post-exposure prophylaxis

6 Division Name or Footer



Nail gun malfunction



7 Division Name or Footer



“Playing catch with the dog”



Lateral View



s/p debridement at OSH



s/p Meatoplasty and Advancement



One Month Later



Two Months Later



Key Principle

- Wash out and primary wound closure (if possible) should be performed, even in contaminated wounds
- Preserve all viable tissue to facilitate reconstruction



"I made a mistake"



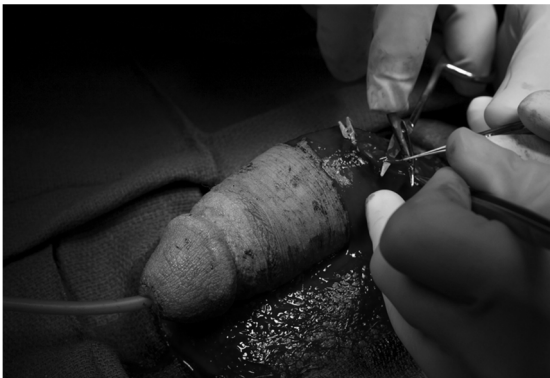
Macroreplantation



Dartos Reapproximated Ventrally



SP Tube Placed



10 hours postop



24 hours after surgery



POD 14



s/p Circ, Perimeatal Debridement;
Cysto→ Urethra Viable, Foley Removed



Retrograde Urethrogram



Week 4: Further Debridement



Week 5: 5 Days s/p STSG



Skin grafts in genital reconstruction

- Penis:
 - Thick (14/1000 or higher) split thickness skin graft on penis
 - Avoid meshed grafts (poor cosmesis)
- Scrotum and perineum
 - Meshed or unmeshed STSG
 - Wound vac to help secure the skin graft

34 Division Name or Footer



2 months after initial injury

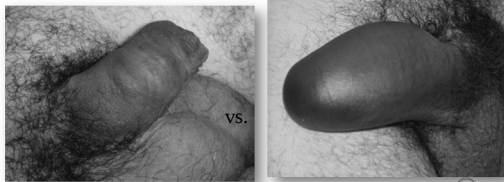


Penile Fracture



Low vs. High Clinical Suspicion

- Things to consider in history and PE...
 - **Immediate detumescence**
 - Inability to achieve erections after event
 - Severe pain
 - Changes in corpora noted on exam
 - Significant edema/hematoma

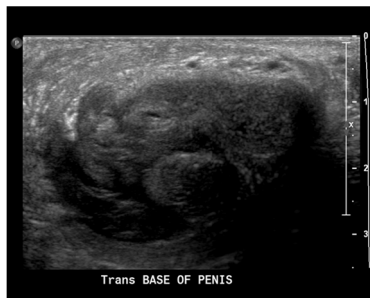


Use of Ultrasound

- 150 patients from Jan 1997 to Nov 2009
- Divided into two study groups based on clinical presentation and imaging results
 - G1: **low** suspicion (25 patients)
 - All patients underwent **conservative management (u/s)**
 - G2: **high** suspicion (125 patients)
 - All patients underwent **surgical exploration**
- All patients in G1 (25 patients) underwent US
 - **Ruled out PF in 100%**
 - All managed with painkillers/anti-inflammatories without hospitalization
- 12 /125 patients in G2 -- US for "doubtful dx"
 - 9 rupture of corpus cavernosum (75%)

Koifman, et al. Urology, 2010

Right corporal disruption w/ adjacent hematoma



Repair Via Penoscrotal approach

- Most fractures are ventral, at the base of penis.
- Urethral injuries almost always occur with bilateral corporal rupture
- Circumcising incision provides poor exposure to proximal corpora
- Penoscrotal approach allows use of the lonestar retractor
- If injury is completely dorsal, can convert incision into "T" and deglove

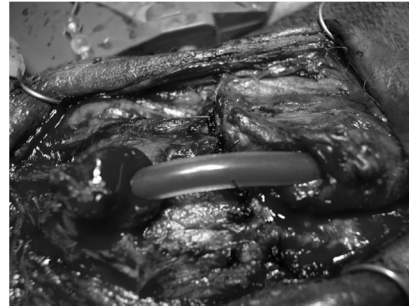
Complete Urethral Rupture & Fracture of Both Corpora



43 Division Name or Footer



Corpora Repaired



Urethra Mobilized & Repaired

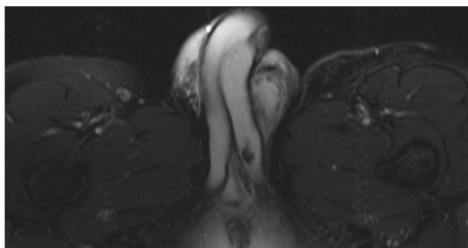


Use of Ultrasound – Penile Fracture

- Good when PE equivocal → can help to **confirm questionable dx** prior to exploration
 - Identifies location of fracture to help select choice of surgical approach.
- Good to r/o fx in patients with low clinical suspicion
- Non-invasive, low-cost
- Widely available



MRI for penile fracture



Timing of Penile Fracture Repair?

- 180 patients Jan 1986 - May 2010
- Divided into two study groups
 - Group I: “**Early**” presentation, <24 hours
 - Group II: “**Delayed**” presentation, >24 hours
 - No difference in etiology, clinical presentation, surgical findings, and incidence of urethral injury
- Mean follow-up time:
 - Group I: 105 months
 - Group II: 113 months



Timing of Repair - Results

- After long-term f/u, 35 patients (19.4%) had complications:
 - Pain on erection (1.4%)
 - Deviation on erection (13.9%)
 - Erectile dysfunction (13.4%)
 - Palpable plaques (12.9%)
- **NO difference** in complications

El-Assmy, et al., 2011



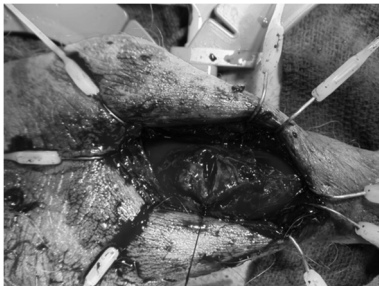
Timing of Repair

- Patients presenting **up to 7 days** after penile fracture can be managed surgically with **similar outcomes** to patients with immediate repair
- US showed site of tear in 53/58 (93%)

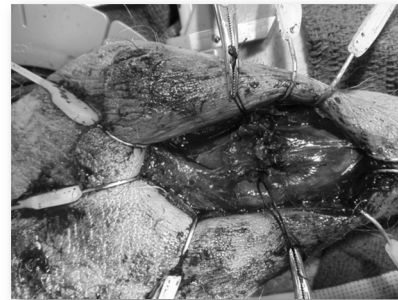
El-Assmy, et al., 2011



Exploration 5 days after injury



Corporal repair



Scrotal injury

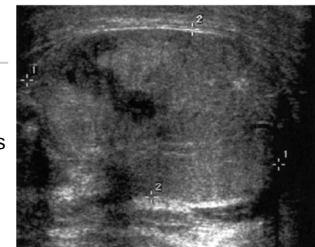
- Penetrating
 - Exploration if dartos is violated
 - Ultrasound controversial
- Blunt
 - Ultrasound to evaluate testicular rupture
 - Exploration for testicular rupture

53 Division Name or Footer



Ultrasound

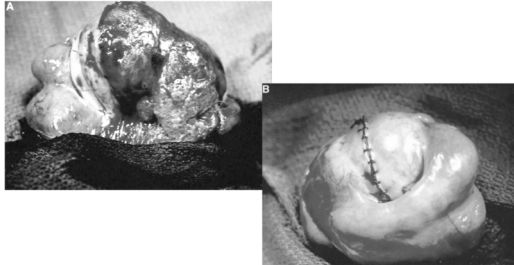
- Heterogeneous echo of testicular parenchyma with loss of contour
- Tunica albuginea rupture



J Urol 2006 , 175: 175



Testicular Repair



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Tunica vaginalis graft



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Scrotal skin defects

- Primary closure typically possible due to elasticity of scrotal skin

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Female genital trauma

- Less common
- Blood at vaginal introitus
- Suspicion for sexual abuse
- Vaginal smear to evaluate for spermatozoa
- Evaluate for concomitant bladder, rectal injuries.
 - CT/MRI
- Primary closure of vaginal lacerations to reduce fistula formation

60 Division Name or Footer

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Injury	Screening Imaging	Intervention
Penis (blunt)	Ultrasound/MRI	Immediate Repair (up to 1 week)
Penis (penetrating)	None vs CT	Immediate Repair
Scrotum	Ultrasound	Repair vs observation
Vas deferens	Intraop finding	Ligate Vas, Delayed VV
Anterior Urethra (usually associated w/ penis or scrotum)	RUG	Immediate Urethroplasty

Immediate	Conservative
Penile injury (fracture, penetrating)	Blunt penile injury without fracture or urethral involvement
Penetrating scrotal injury	Blunt scrotal injury without testicular injury
Blunt scrotal injury w testicular involvement	
Anterior urethral injury	
	



Management of Upper Urinary Tract Obstruction

Stephen Y. Nakada, MD

Disclosures

Stephen Y. Nakada, MD. FACS, FRCS (Glasg.)

- Boston Scientific - Consultant



Upper Tract Obstruction

- Evaluation of Upper Tract Obstruction
- Ureteropelvic Junction Obstruction
- Retrocaval Ureter
- Ureteral Stricture Disease
- Ureteroenteric Anastomotic Stricture
- Retroperitoneal Fibrosis

Upper Tract Obstruction

- **Evaluation of Upper Tract Obstruction**
- Ureteropelvic Junction Obstruction
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Evaluation of UTO

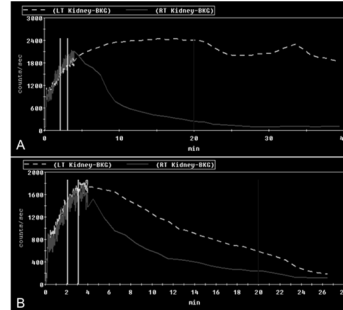
- CT- low dose, CT urography
- IVU
- Ultrasound
- Retrograde pyelogram
- Diuretic Renography
- Whitaker test



CT



Diuretic renography



Whitaker Test

- Useful with concomitant stones
- Ultimately accurate
- Requires NT and foley catheter
- Must be dynamic

Upper Tract Obstruction

- Evaluation of Upper Tract Obstruction
- **Ureteropelvic Junction Obstruction**
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Ureteropelvic Junction Obstruction

- Intrinsic, aperistaltic segment
- Role of crossing vessels
- Diagnosis: renography, CT angiography, CT urography
 - Roles for crossing vessel, UPJ anatomy
 - Ultrasound; prenatal value and multicystic kidney
- Renography
 - Quantitative, functional status, follow up

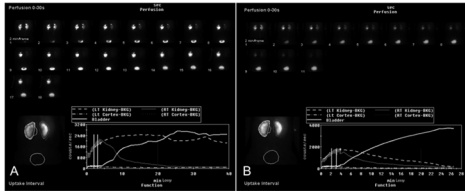
UPJ Etiology

Lack of Interstitial cells of Cajal
Aperistaltic segment
Congenital
TGFB, EGF, NO as causes



UPJO: Indications

- Symptomatic obstruction
- Impairment of renal function
- Stone disease or UTIs
 - Causal hypertension



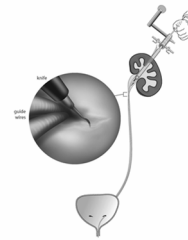
UPJO- Intervention

- Dismembered pyeloplasty
- Endopyelotomy
- Laparoscopic pyeloplasty
- Robotic assisted laparoscopic pyeloplasty (RALP)

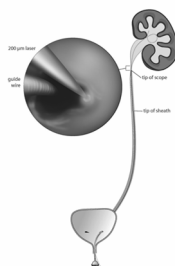
Endourologic Mgt for UPJO

- Endopyelotomy
 - Antegrade
 - Retrograde
- Crossing vessels
 - Data suggest success rates altered by CV, degree of hydronephrosis
 - Requires high-dose axial imaging or angiography
- Concomitant stones
 - Antegrade approach favored

Antegrade EP



Retrograde EP



UPJO with stones

- PCNL and antegrade endopyelotomy
 - Concerns of inflammation at the UPJ
 - Need to assess UPJ once stone removed
 - Option for Whitaker test with existing NT

Secondary interventions

- Open or lap/robotic for failed endopyelotomy
- Endopyelotomy for failed open or lap/robotic
 - Data quite good (>90%) for EP following pyeloplasty

Pyeloplasty

- Open
- Laparoscopic
- Robotic

Open Pyeloplasty

- Flank incision
- 95% success rate
- Effective in children
- Dorsal lumbotomy approach in select cases
- In adults, an approach in centers lacking MIS expertise

Laparoscopic Pyeloplasty

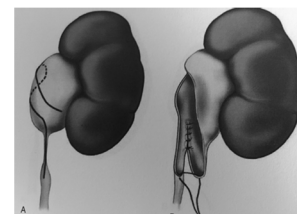
- Pioneered by Kavoussi
- Success rates >90%
- Requires laparoscopic suturing, knot-tying
- Optional mesenteric approach
- Eliminates concerns of crossing vessels
- Allows for management of stones concomitantly

Robotic pyeloplasty

- Logical extension of the procedure from laparoscopy
- Allows more surgeons to perform the procedure
- Opens options for single incision
- Similar operations and approaches to repair UPJ; Success equivalent
- Cost

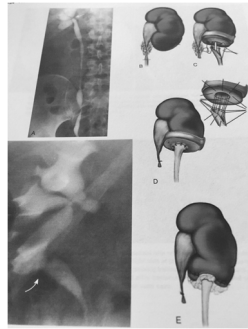
UPJ repairs

- Dismembered
- Foley YV plasty
- Fenger plasty
- Vertical flap



Ureterocalicostomy

- Options for UPJO and PUS with small renal pelvis
- Also for HSK for dependent drainage
- Well accepted salvage procedure
- Assess function of ipsilateral moiety



Upper Tract Obstruction

- Evaluation of Upper Tract Obstruction
- Ureteropelvic Junction Obstruction
- **Retrocaval Ureter**
- Ureteral Stricture Disease
- Ureteroenteric Anastomotic Stricture
- Retroperitoneal Fibrosis

Retrocaval Ureter

- Rare anomaly, persistence of the lower cardinal veins during embryologic development
- Diagnosis by CT
- Treatments
 - If indicated, open or robotic approaches successful

Upper Tract Obstruction

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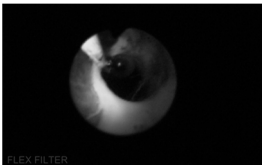
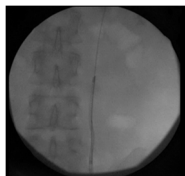
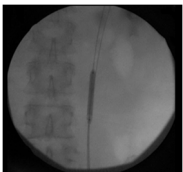
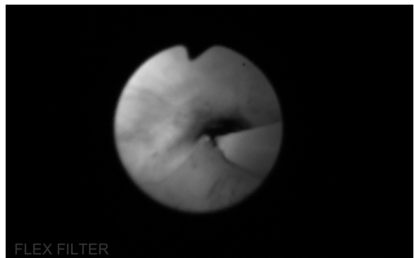
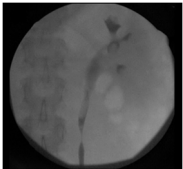
Ureteral Strictures

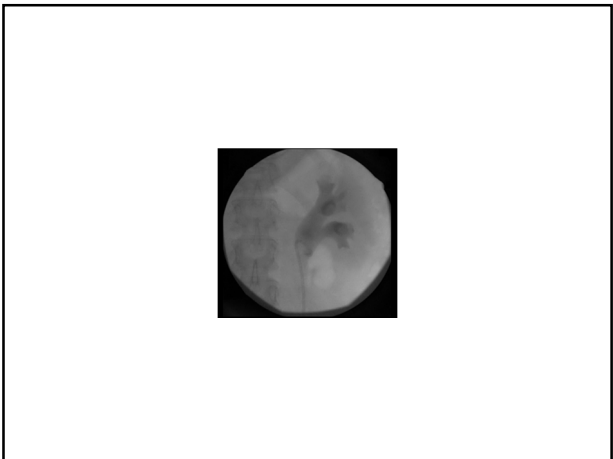
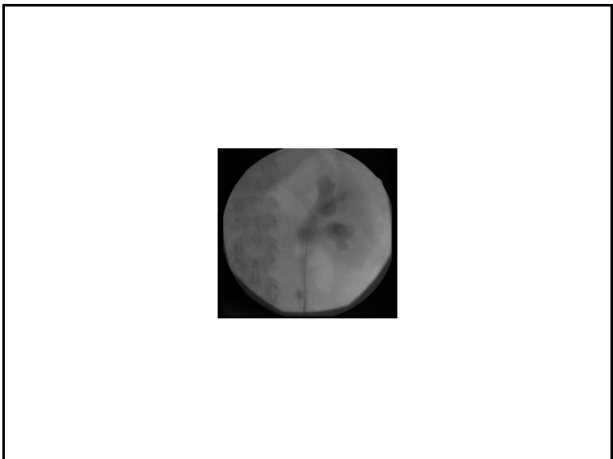
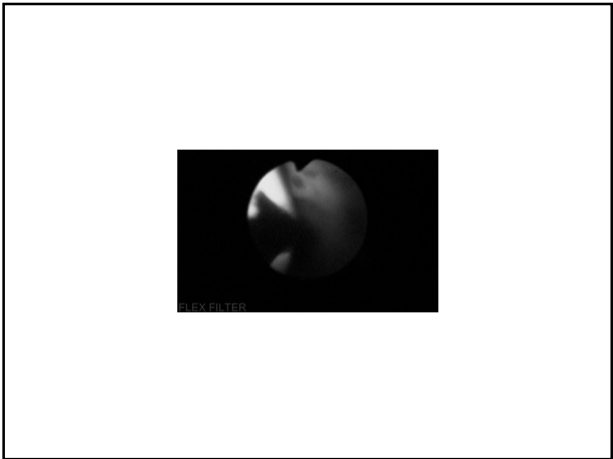
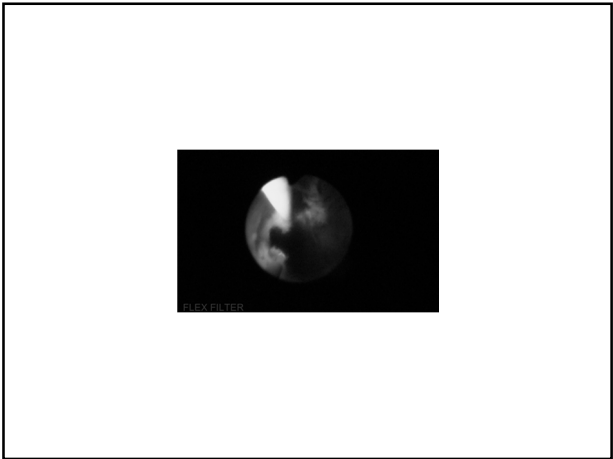
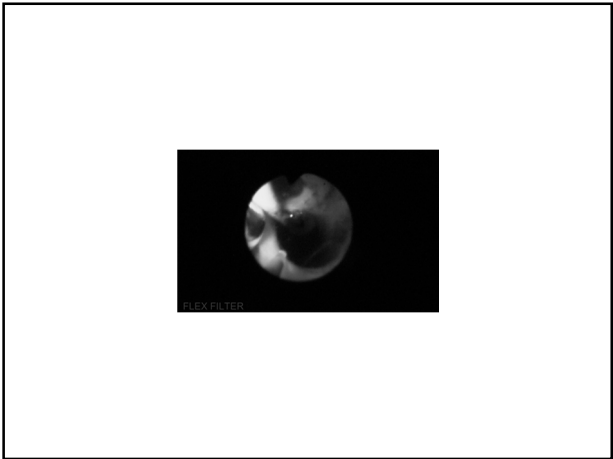
- Diagnosis
 - Retrograde pyelogram
 - Diuretic renography with split function
- Indications
 - Symptoms, infections
 - Renal functional loss
 - up to 2 cm managed endoscopically
 - 20% function

Treatment options

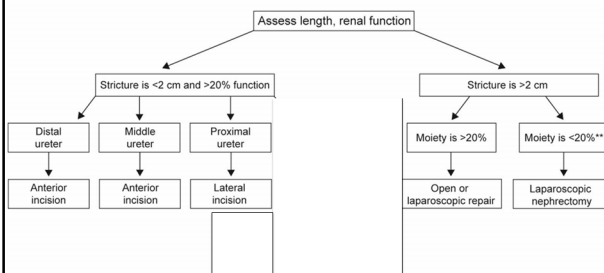
- Balloon dilation- low longterm success
- Endoscopic incision
 - Laser
 - Cold knife
 - Cutting balloon catheter (less used due to risk of bleeding and improved lasers)

Endoincision





Optimal therapy for benign ureteral strictures*



*Consider balloon if transplant on immunosuppression
 **Pediatric and younger patients may warrant repair

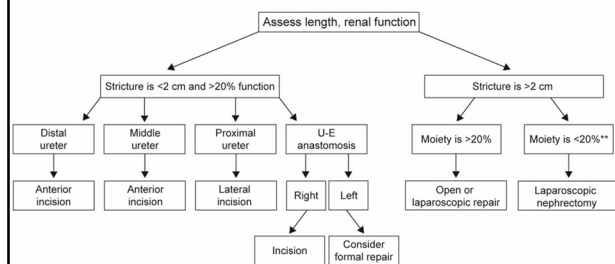
Upper Tract Obstruction

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- **Ureteroenteric Anastomotic Stricture**
- Retroperitoneal Fibrosis

UE Strictures

- Success rates poor bilaterally
- Right side better than left
- Assess for TCC
- Always do a renal scan
- Retrograde procedures challenging

Optimal therapy for benign ureteral strictures*



*Consider balloon if transplant on immunosuppression
 **Pediatric and younger patients may warrant repair

Bridging Longer defects

- Ureteroneocystotomy
- Boari flap
- Ureteroureterostomy
- Trans UU
- Ileal ureter
- Autotransplantation



Upper Tract Obstruction

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- **Ureteroenteric Anastomotic Stricture**
- **Retroperitoneal Fibrosis**

Retroperitoneal Fibrosis(RPF)

- Presentation-inflammatory disease in the RP causing compression of the structures including the ureters, L4-5
- 70% idiopathic, but it is considered a chronic periaortitis, a large vessel vasculitis
- 30% of patients have a cause, such as methysergide use, ergot alkaloids, B blockers, or malignancy

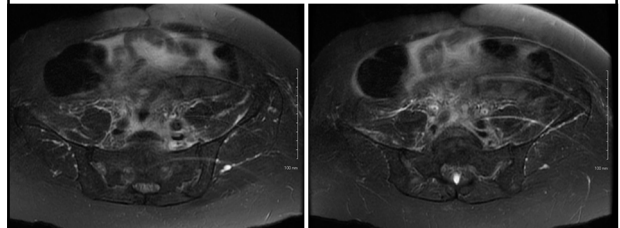
RPF evaluation

- ESR, CRP elevation in aortitis group 30-50%
- CT reveals hydronephrosis
- Renal scan
- MRI low signal intensity on T1, higher in active disease on T2
- Gadolinium enhancement a sign of active disease
- PET scan

CT diagnosis



MRI



RPF Management

- Decompression, stent or NT when symptoms of obstruction
- Postobstructive diuresis a concern
- Medical management
 - Steroids 80% response, follow ESR, CRP, MRI
 - 2 year therapy typically, remove drains, then taper
 - Immunosuppressive agents are second line, as 50% of steroid responsive cases recur during tapering
 - Cyclosporine, cyclophosphamide, azathioprine

Surgical Management PRF

- Ureterolysis
 - Mass biopsies
 - TP approach
 - Intraperitoneal placement of the ureters
 - Omental wrap
- Open, lap or robotic
 - Good success up to 90% at 30 months
 - Lap equal to open with shorter recovery
 - Robotic also reported, 84% with shorter recovery
- Autotransplantation

Evaluation and Management of the Kidney Stone Patient: an Update

David S. Goldfarb, M.D.
david.goldfarb@nyumc.org



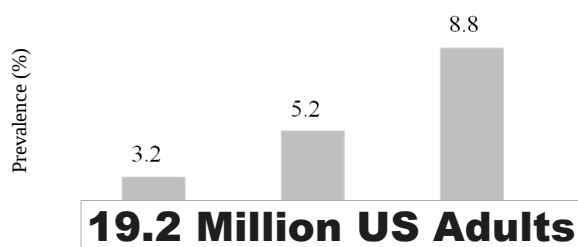
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Disclosure

- Consultant:
 - Allena, Alnylam, Retrophin, The Ravine Group
- PMHx: CaOx stones

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US Population Prevalence of Nephrolithiasis (NHANES 1976-2010)



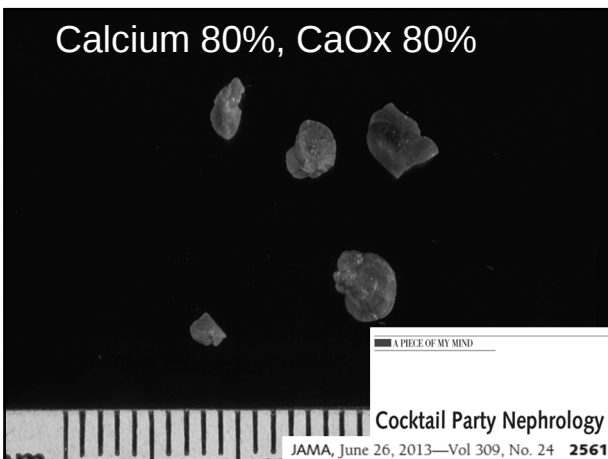
Stamatelou, KI, 2003; Scales, Eur Urol, 2012

Prevalence and Recurrence of Stones

- Lifetime prevalence:
 - 12% in American men
 - 7% in American women
- Recurrence rates:
 - 30% at 5 years
 - 50% at 10 years
 - 80% at 20 years

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Calcium 80%, CaOx 80%



Cocktail Party Nephrology

JAMA, June 26, 2013—Vol 309, No. 24 2561

Calcium phosphate (hydroxyapatite)
20% of calcium stones = 15%



Consider:
Primary hyperparathyroidism
Renal tubular acidosis

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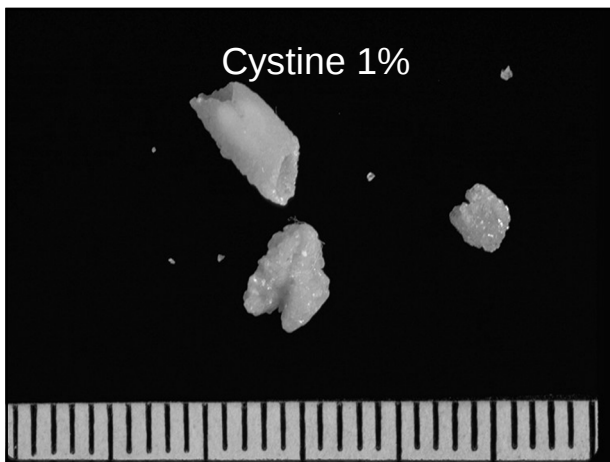
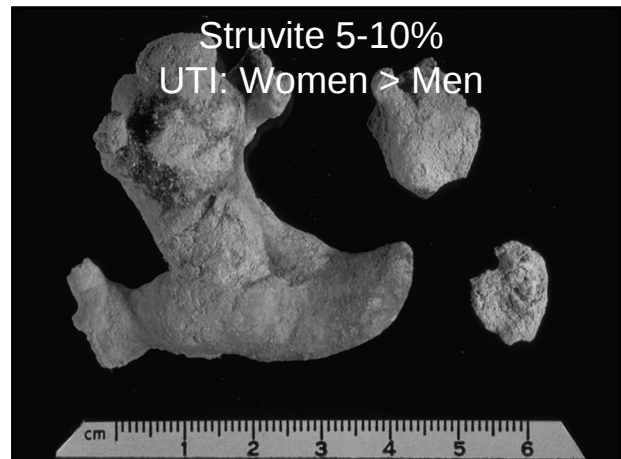
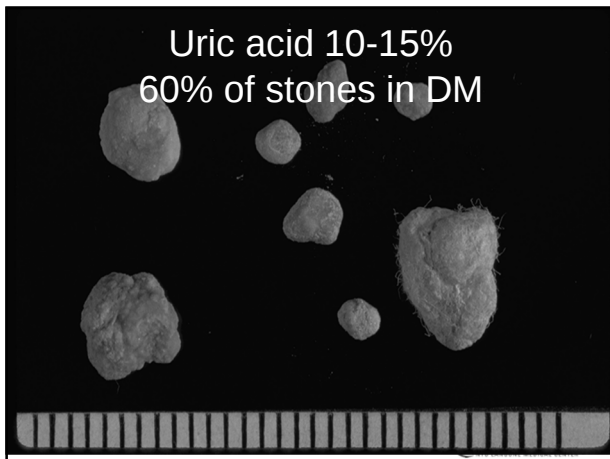


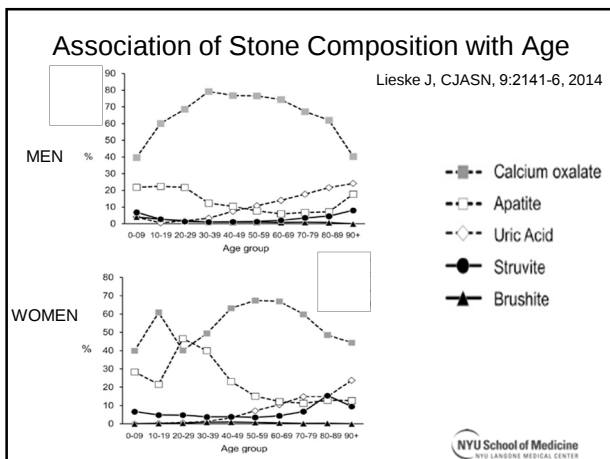
Table 1. Distribution of stone type analyzed during calendar year 2010 (n=43,545)

Stone Type	Number	Percent
Calcium oxalate	29,319	67.3
Apatite	7000	16.1
Uric acid	3611	8.3
Struvite	1318	3.0
Brushite	374	0.9
Cystine	151	0.35
Ammonium urate	105	0.20
Artifact	1393	3.2
Other	171	0.4
Drug	60	0.1
Sodium/potassium urate	42	0.1
Dihydroxyadenine	1	0.002

Only the first stone submitted per individual was included.

Lieske J, CJASN 9:2141-6, 2014

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Urinary Risk Factors for Calcium Stone Disease

- Hypercalciuria
- Hyperoxaluria
- Hypocitraturia
- Hyperuricosuria
- Low urine volume
- (too much crystal promoters)
- (too little crystal inhibitors)

AUA Guidelines

Medical Management of Kidney Stones: AUA Guideline

Margaret S. Pearle, David S. Goldfarb, Dean G. Assimos, Gary Curhan, Cynthia J. Denu-Ciocca, Brian R. Matlaga, Manoj Monga, Kristina L. Penniston, Glenn M. Preminger, Thomas M. T. Turk and James R. White

<http://www.auanet.org/education/guidelines/management-kidney-stones.cfm>.



Evaluation of Patient with First Stone Episode

- **History:** medications, occupation, family history of stones or other kidney disease (e.g. PKD), inflammatory bowel disease (e.g., Crohn's disease).
- **Diet:** intake of protein, purines, sodium, fluids, oxalate, and calcium
- **Imaging:** are there other stones present?
 - Or anatomically important kidney disorders, e.g. PKD, MSK



Evaluation of Patient with First Stone Episode

- **Serum:**
 - Electrolytes, creatinine
 - Hypercalcemia, values ≥ 10.0 mg/dl
 - Consider:
 - primary hyperparathyroidism
 - Sarcoidosis
 - CYP24A1 mutations and vitamin D intake
 - $[\text{HCO}_3^-] < 22$ meq/L
 - Consider distal renal tubular acidosis
 - Mg, PO_4 , uric acid



Evaluation of Patient with First Stone Episode

- **Urinalysis:**
 - high urine pH: RTA
 - high urine pH: struvite stones
 - low urine pH: uric acid stones
- **Urine culture** if indicated
- **Stone analysis** (OR do qualitative cystine screening at least once in children-age 50)
 - X-ray diffraction
 - Infrared spectroscopy



Medications and Stones

- Topiramate, acetazolamide
- Atazanavir
- Vitamin C
- Felbamate
- Triamterene
- Guafenesin



EVALUATION

5. Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers (Standard: Grade B)

Grade B evidence: "moderate"



EVALUATION

6. Metabolic testing should consist of 1 or 2, 24-hr urine collections obtained on a random diet (Expert Opinion)

Urine should be tested for:

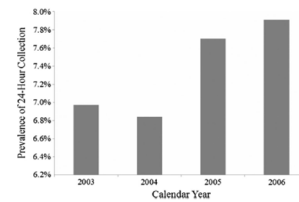
Volume	Citrate
pH	Sodium
Calcium	Potassium
Oxalate	Creatinine
Optional (helpful): SO_4 , Urea, SS	

- If urine oxalate excretion ≥ 75 mg/d in adults, refer for genotyping or specialized urine testing

Prevalence of 24-Hour Urine Collection in High Risk Stone Formers

Jaclyn C. Milose, Samuel R. Kaufman, Brent K. Hollenbeck, J. Stuart Wolf, Jr. and John M. Hollingsworth*

From the Divisions of Endourology and Health Services Research, Department of Urology, University of Michigan, Ann Arbor, Michigan



Multivariable regression provider factors associated with 24-hour urine collection

Seen by:	OR (CI)
Nephrologist	2.9 (2.3-3.7)
Urologist	3.9 (3.5-4.3)

Prevalence of 24-hour urine collection in patients at high risk for stone recurrence.

J Urol 191:376-380, February 2014



The Journal of Urology

Available online 13 October 2016

In Press, Accepted Manuscript — Note to users



The role of the 24-hour urine collection in the prevention of kidney stone recurrence

Ryan S. Hsi, Thomas Sanford, David S. Goldfarb, Marshall L. Stoller
[Show more](#)

24h Urine: Pros



- Objective, quantifiable data
- Provides adherence data
- Provides answers to patient
- More convenience than ever!
- Limit prescription of diet and meds to specific issues
- Potential surrogate for outcome

24h Urine: Cons



- Complexity in interpretation
- Limited ability to predict recurrence
- Inconvenient for some
- Requires repeat testing
- Cost

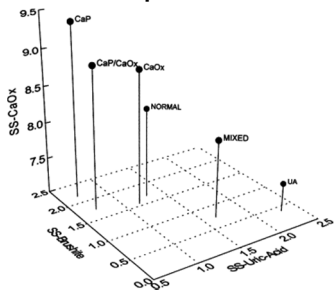
Which urine to review?

- Weekday/Work day vs Weekend
- Or would spot urines be useful?
 - Any: It's a disease of concentration
 - Post-prandial
 - Night time

Cabbies holding in their urine to a dangerous degree



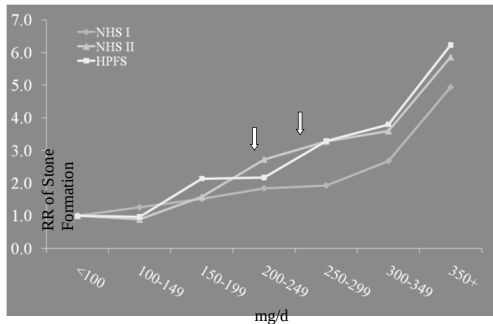
SS correlated with CaOx, CaPhos and uric acid stone composition



Male stone formers plotted on 3 axes of SS

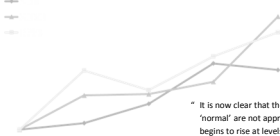


24 Hour Urine Calcium



Cases: 2237; Controls: 1113

24 Hour Urine Oxalate



Cases: 2237; Controls: 1113

The Exposome for Kidney Stones

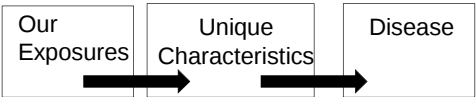
Urinary Stone Disease
Research Challenges and Opportunities

April 1 - 2, 2015

NIH Campus
Natcher Conference Center
Building 45, Auditorium
Bethesda, MD



Exposome: Exposure to Disease



Modified from
<http://www.cdc.gov/niosh/topics/exposome/>



Urol Res (2004) 32: 41-43
DOI 10.1007/s00240-003-0373-7

ORIGINAL PAPER

M. A. Chang · D. S. Goldfarb

Occupational risk for nephrolithiasis and bladder dysfunction in a chauffeur

- A 54-year-old professional driver not permitted to urinate on long drives
- Urodynamics: hypocontractile dilated bladder
- Ultrasound: bilateral asymptomatic stones





DISEASE STATE REVIEW

Taxi Cab Syndrome: A Review of the Extensive Genitourinary Pathology Experienced by Taxi Cab Drivers and What We Can Do to Help

Alon Y. Mass, MD,¹ David S. Goldfarb, MD,² Ojas Shah, MD¹
¹Department of Urology, NYU Langone Medical Center, New York, NY; ²Nephrology Section, New York Harbor VA Healthcare System and Nephrology Division, NYU Langone Medical Center, New York, NY

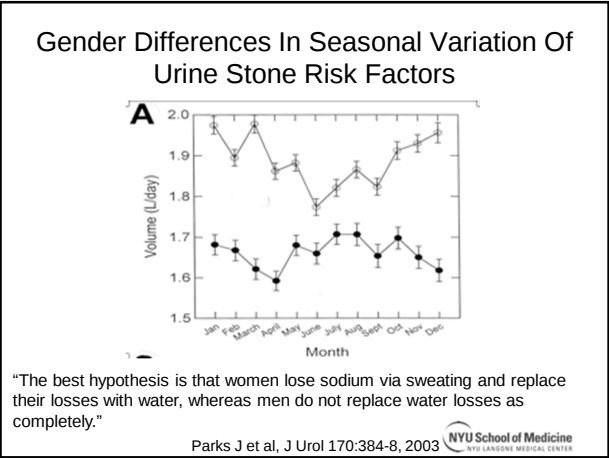
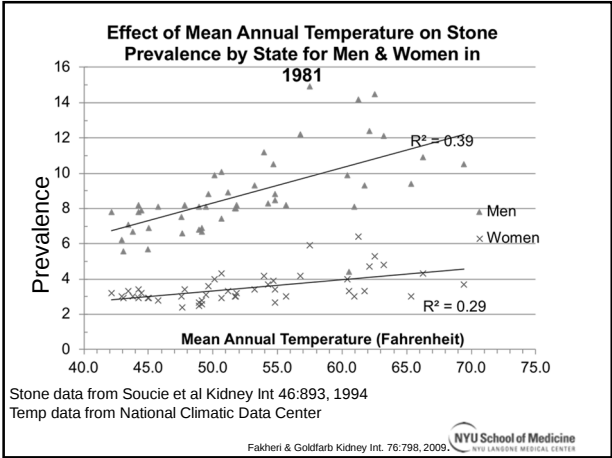
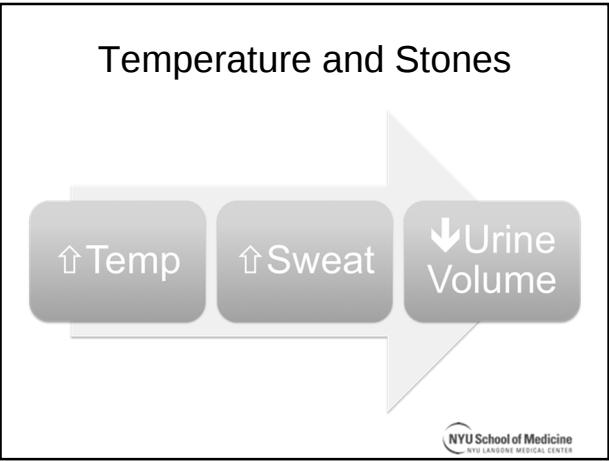
Rev Urol 16:99-104, 2014

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Effect of Work Location on Kidney Stones in Healthcare Professionals
3,921 randomly selected Mayo employees

	OR Staff	Non-OR Staff
History of stones	14.6%	9.7%
Mean # stones	1.8	1.3
Daily fluid intake < 1.8L	63.1%	48%
Physicians with stones	17.4%	9.7%
HR for working in OR: 1.43		

Linder BJ, Urolithiasis, 41:327-331, 2013 NYU School of Medicine
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Climate-related increase in the prevalence of urolithiasis in the United States

Tom H. Brikowski^{a,*}, Yair Lotan^a, and Margaret S. Pearle^a PNAS | July 15, 2008 | vol. 105 | no. 28 | 9841-9846

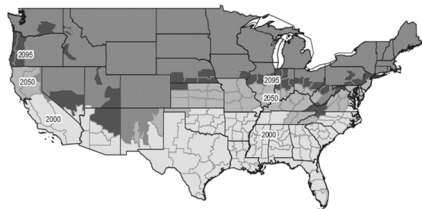


Fig. 3. Predicted growth in high-risk stone area (stone belt; risk ratio ≥ 1.2) vs. time, for 2000 (yellow), 2050 (orange), and 2095 (red); linear model. At 2000, 41% of the population is within a high-risk zone, 56% at 2050, and 70% at 2095, based on year 2000 population distribution.

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Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Hypothesis: Urbanization and exposure to urban heat islands contribute to increasing prevalence of kidney stones

David S. Goldfarb^{a,b,*}, Jacqueline Hirsch^b

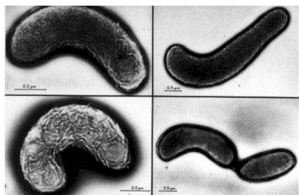
^a Nephrology Section, New York Harbor VA Healthcare System, New York, NY, United States

^b NYU School of Medicine, New York, NY, United States

Medical Hypotheses 85:953–957, 2015

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Oxalobacter formigenes

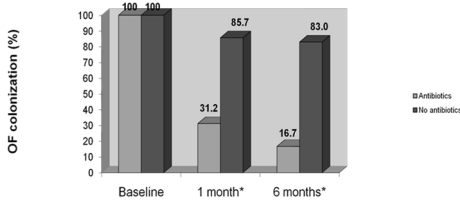


- Gram negative, obligate anaerobe
- One substrate: Oxalate
- Presence associated with diminished Uox
- Absence associated with hyperoxaluria

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Antibiotics for HP Eliminated Colonization with OF

- Actual prevalence rate: about 32%



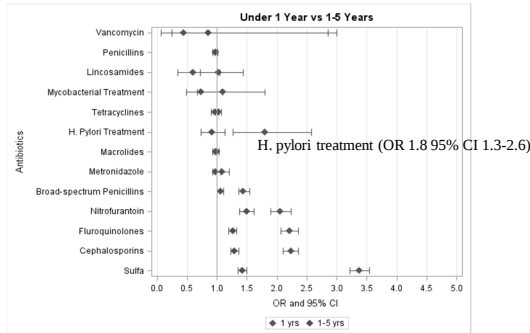
* P = 0.01, Fisher exact test

Ab: mostly amoxicillin and clarithromycin; some metronidazole

Khariamb et al, J Endourol, 2012

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Risk of stones with antibiotics



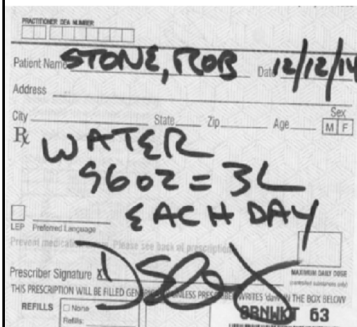
The Health Improvement Network (THIN) database
N = 26,466 patients with stones and 264,647 matched controls
Tasian G et al, AUA 2017

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Prevention of Recurrent Calcium Stones

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The Powerful Stuff: Intuitive, Cheap, Effective, Safe, Legal



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Non-specific Prevention of Calcium Oxalate Stones

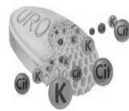
- Increase urine volume to ≥ 2 liters/d
- Supported by RCT
- Emphasis on output, not intake
 - more with heat, exercise
- All day long
- Before sleeping
- Coffee and beer are protective!

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What is the treatment for low urine volume?
What is the treatment for **occupational kidney stones**?

Potassium citrate:

- Surgeon: before going to the OR
- Baseball player: before going on the field
- Teacher: before class
- Cab driver: before getting into the taxi
- Steel worker: before entering work place
- Everyone: at bedtime



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Diet: Relative risk of symptomatic kidney stones
according to dietary calcium intake

Dietary Intake mg/d	Quintile	1	2	3	4	5
Calcium		< 605	605-722	723-848	849-1049	> 1050
RR stones		1.0	0.71	0.64	0.61	0.56

N =45,510 men

Curhan NEJM 328:833, 1993

- Similar result in women: Curhan, Ann Int Med 126:497, 1997

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Increasing Dietary Calcium Intake for Prevention of Ca Stone Recurrence

- Borghi *et al* NEJM 346:77 (2002)
- 60 men in each arm: men with at least 2 episodes of calcium stones and hypercalciuria (>300 mg/day)
- 1) "normal" amount of calcium (30 mmol per day) but reduced amounts of animal protein (52 g per day) and salt (50 mmol of sodium chloride per day)
- 2) traditional low-calcium diet, which contained 10 mmol of calcium per day
- Outcome: stone recurrence either silent or symptomatic

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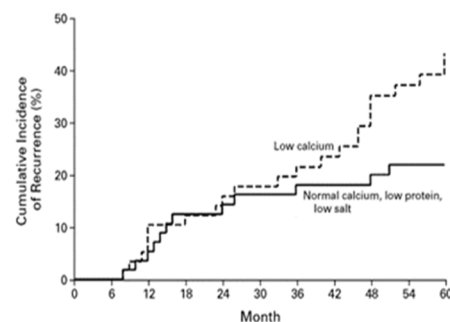


Figure 2. Kaplan-Meier Estimates. The relative risk of a recurrence in the group assigned to the normal-calcium, low-protein, low-salt diet, as compared with the group assigned to the low-calcium diet, was 0.49 (95 percent confidence interval, 0.24 to 0.98; P=0.04).

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Prevention of Calcium Oxalate Stones

- Calcium restriction is out!
- Not proven to reduce stone recurrence
- Associated with bone demineralization

Calcium intake 800-1200 mg per day

Pharmacologic therapy: thiazides

- Chlorthalidone (indapamide)
- Lower salt intake
- Supplement with K citrate
 - NO triamterene (e.g. Dyazide, Maxzide)
 - Amiloride 5-10 mg once or twice a day for K sparing
 - Spironolactone

Other benefits of thiazides

- As effective as any other class for HTN
- Cheaper!
- Best drugs for HTN in the elderly
 - For systolic HTN
- Associated with increased bone density
 - Fewer fractures

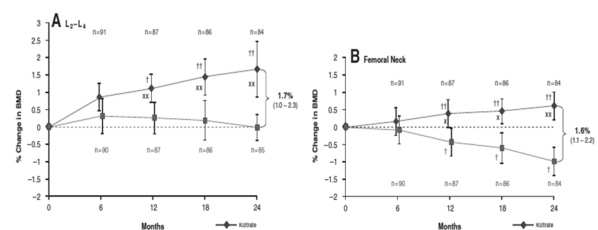
Thiazides

- If UCa shows no “cut-point” AND
- Thiazides are effective no matter the UCa....
- AND drugs are
- Effective
- Inexpensive
- Increase life expectancy
- Increase BMD and reduce fracture rate....
- Why not just give them to everyone

Drug Therapy Calcium Oxalate Stones

- Hypocitraturia
 - Potassium citrate: 20-40 meq bid
 - NOT sodium citrate: inc. UCa
 - Use in “non-selected” cases

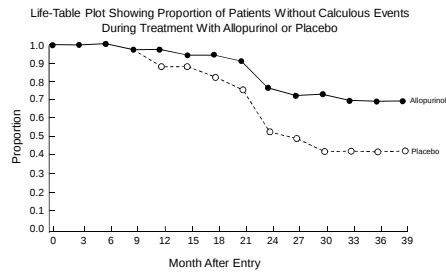
Effect of Potassium Citrate on Bone Density, Microarchitecture, and Fracture Risk in Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial



K citrate 60 meq qd with calcium and vitamin D

Jehle S et al, JCEM epub 11/15/2012

New stone events in: 18 participants on placebo
9 receiving allopurinol



Allopurinol 300 mg in calcium stone formers with UCa < 250 mg/day

Ettinger et al; NEJM. 315:1386 (1986).

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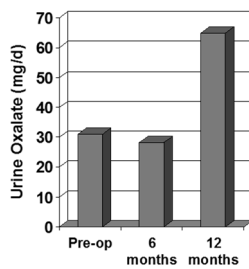
Hyperoxaluria

- Oxalate is an important determinant of SS
- Yet no study of the effect of lowering urinary oxalate excretion on stone outcomes has been performed
- **Increase dietary calcium intake if low**
- Allena-177: oxalate decarboxylase



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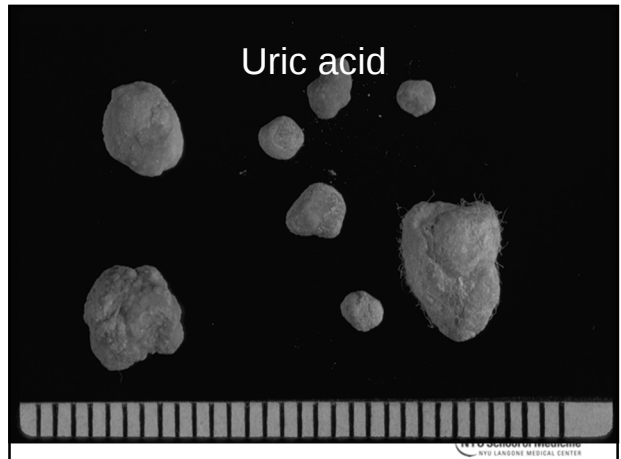
Gastric Bypass and Hyperoxaluria: The Mayo Clinic Experience



Sinha MK et al, Kidney Int 72:100, 2007

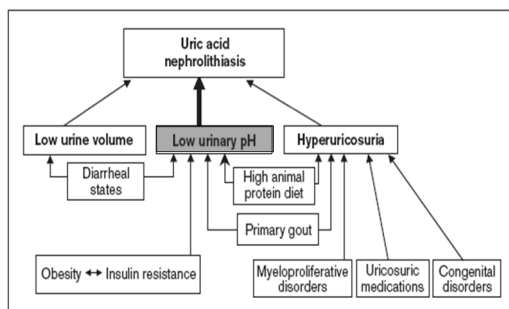
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Uric acid



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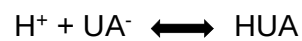
Three Contributors to Uric Acid Stones



Maalouf NM, Curr Opin Nephrol Hypertens 2004, 13:181

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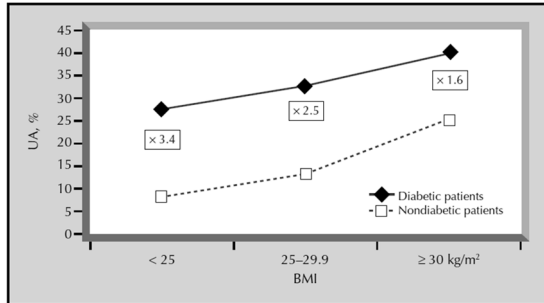
Titration of Uric Acid



$$\text{pKa} = 5.35$$

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Proportion of Stones Composed of Uric Acid With Increasing BMI



Daudon; Curr Diab Rep. 7:443-448 (2007).

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Etiology of Uric Acid Stones

- Insulin resistance → impaired ammoniagenesis
- Impaired ammoniagenesis → “unduly acid urine”

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Treatment of uric acid stones

- Alkalinize urine with potassium citrate
- Na citrate, NaHCO_3 if necessary
- Allopurinol is ineffective if UpH is not increased: reserve for patients with recalcitrant stones, difficulties alkalinizing

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Rates of stones and cost before and during treatment

	Before Rx	During Rx
	#/1000 pt-yrs	#/1000 pt-yrs
Stones	1752	382
Urologic Intervention	198	106
Hospitalization	375	90
\$/1000 pt-yrs	\$4.5M	\$1.3M

N=1092

Parks JH, Coe FL. Kidney Int 50: 1706, 1996.

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Classical Twin Study Viet Nam Era Twin Registry

		Twin 1	
		Has	Does not have
Twin 2	Has	a	b
	Does not have	c	X

$$\text{Concordance} = \frac{a}{a + b + c}$$

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Results: Classical Twin Study

	Concordant Pairs	Discordant Pairs	Rate of Concordance
Dizygotic Twin Pairs	17	163	9.4%
Monozygotic Twin Pairs	39	163	19.3%

p = 0.007

Results attributable to:

Heritability 56%

Environmental effects 44%

Goldfarb DS, et al Kidney Int 67:1053-1061, 2005

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Kidney Stones in Women and Men: Washington State Twin Registry

	MZ Women	DZ Women	MZ Men	DZ Men
Concordant	21	5	20	5
Discordant	159	188	75	51
Concordance	0.21*	0.10	0.35*	0.16

Heritability 45% in women, 66% in men, *p < 0.05.

Goldfarb DS, Noonan C, Goldberg J, ASN 2012



Genetics of Calcium Stones

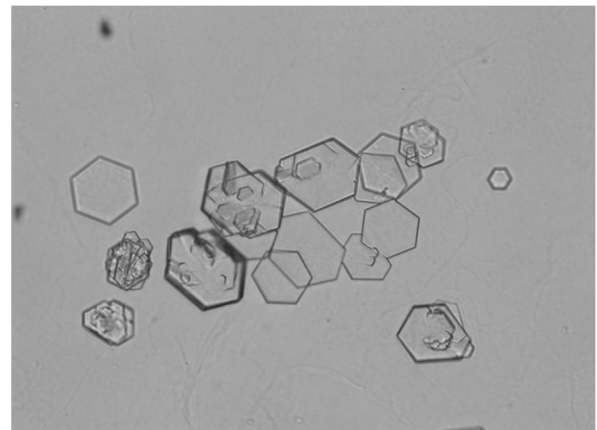
- Gene responsible for hypercalciuria is NOT:
 - Vitamin D receptor
 - Interleukin-1 Receptor
 - CLCN5
- Some data for SNPs of:
 - CaSR
 - TRPV5
 - CLDN 14, 16, 19



RARE KIDNEY STONE CONSORTIUM

Dawn Milliner, MD (PI)
John Lieske, MD
David S. Goldfarb, MD
Lada Beara-Lasic, MD
Viðar Eðvarðsson, MD
Runólfur Pálsson, MD

Mayo Clinic: PH
Mayo Clinic: Dent
New York University: Cystinuria
New York University: Dent disease
Landspítali Univ Hosp: APRTd
Landspítali Univ Hosp: APRTd



Pediatr Nephrol. 28:1923-42, 2013

REVIEW

Hereditary causes of kidney stones and chronic kidney disease

Vidar O. Eðvarðsson • David S. Goldfarb •
 John C. Lieske • Lada Beara-Lasic • Franca Anglani •
 Dawn S. Milliner • Runólfur Pálsson

- Cystinuria
- Primary Hyperoxaluria
- APRT deficiency: Dihydroxyadenine Stones
- Dent disease

Acknowledgements



NYU Langone Medical Center

NIDDK
NATIONAL INSTITUTE OF
DIABETES AND DIGESTIVE
AND KIDNEY DISEASES



National Kidney Foundation
serving Greater New York



Surgical Management of Urinary Stone Disease

Peter L. Steinberg, MD
Beth Israel Deaconess Medical Center
Director of Endourology and Kidney Stone
Management
August 6th, 2018

Disclosures

- No financial disclosures
- No conflicts of interest

Learning Objectives

- Describe a general approach to the operative management of urinary stones
- Discuss the pros and cons of ureteroscopy versus shockwave lithotripsy
- Understand the indications for PCNL

Excellent Reference

“Surgical Management of Stones,”

2016 AUA and Endourological Society
Guideline

Overview

- Discussing choice of surgical therapy for different stone sizes and locations
- Indications for surgery
- Timing of surgical intervention
- Management of ureteral and renal stones:
 - SWL
 - URS
 - PCNL

Kidney Stone Epidemiology

(Pearle 2007, Goldfarb 2009; Scales 2012; Krambeck 2014, AUA 2014)

- Prevalence: Appx 10% of adults
- 5.3 billion dollars annually (total cost)
- Incidence 1% of the workforce annually
- 50% second stone in 5-10 years
- Nearly 10-20% require surgery

Indications for Surgery

- Ureteral Stones
 - Failure of observation
 - Intractable symptoms
 - Large stone with low chance of passage
 - Prior decompression without stone passage
 - Travel or other obligations prohibitive
 - AKI
- Renal Stones
 - Large stones
 - Symptomatic
 - Want to avoid colic/passage
 - Travel or professional obligations
 - Nidus for infections
 - AKI

Factors in Choosing Approach

- Location, location, location
 - Ureter: proximal, middle, distal
 - Kidney: pelvis, calyx, lower pole
- Size
 - < 1cm, 1-2 cm, > 2 cm
- Stone characteristics
 - Ca ox monohydrate, uric acid, struvite
- Urinary anatomy
 - Caliceal tic, UPJ-O, urinary diversion

Surgical Techniques

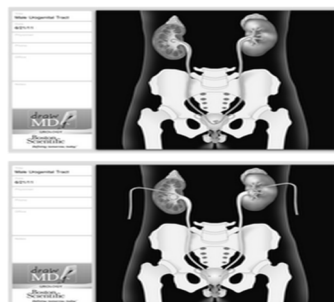
- Shockwave lithotripsy (SWL)
- Ureteroscopy (URS)
- Percutaneous nephrolithotomy (PCNL)
- “Open Surgery”
 - Often done with laparoscopy or robotics
 - Anatomic nephrolithotomy, ureterolithotomy, pyelolithotomy

Timing of Surgical Management

- Acute Management
 - Emergent decompression
 - PCN or Stent
- Semi-elective management
 - Usually ureteral stones
 - Previously stented or PCN placed
- Elective management
 - Usually renal stones

Emergent Decompression

- Intractable pain
- Renal failure
- SIRS/Sepsis
- Solitary kidney



Draw MD, Kutikov et al 2012

Stent vs PCN

(Lipkin BJU 2013)

- Dealer's choice
- Failure rate is 2% (3/130)
- PCN associated with
 - Large stone
 - Longer ICU and hospital stay
- 90% of patients need definitive stone surgery
 - Average of 30 days after decompression

CRP and Decision to Stent

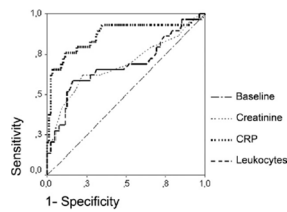


Figure 2. Receiver operating characteristic curves for different variables, including creatinine, C-reactive protein, and total leukocyte count, to assess the need of emergency drainage in patients with renal colic secondary to urolithiasis (AUC: creatinine 68.4%, leukocytosis 68.8%, CRP 86.8%).

The Value of C-reactive Protein Determination in Patients With Renal Colic to Decide Urgent Urinary Diversion
Angulo, Javier C. et al.
Urology, Volume 76, Issue 2, 301-306

Ureteral Stones

AUA Guidelines 2016

- As a rule of thumb:
 - Smaller stones pass at higher rates than larger stones
 - Distal stones pass at higher rates than proximal
- Of stones that pass, 95% pass in 30-40 days of presentation

Negative URS – 10%

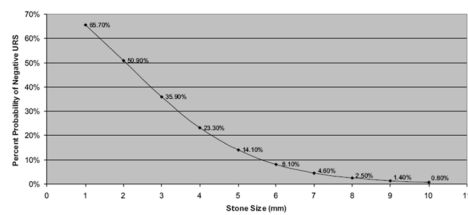


Figure 1. Probability of Negative Ureteroscopy with Respect to Stone Size.

Predictors for Negative Ureteroscopy in the Management of Upper Urinary Tract Stone Disease
Kreshover, Jessica E. et al.
Urology, Volume 78, Issue 4, 748-752

Ureteral Stone Management

Ann Emerg Med 2007, Lotan 2002

- Distal stones = Ureteroscopy
 - SWL less of a role
- Upper ureteral stones: SWL or URS
 - SWL in good candidates
- Large proximal stones/impacted stones
 - Antegrade/PCNL
 - Lap/robotic ureterolithotomy
 - Aberrant anatomy, failures, concurrent procedures

Shift Away from SWL to Ureteroscopy

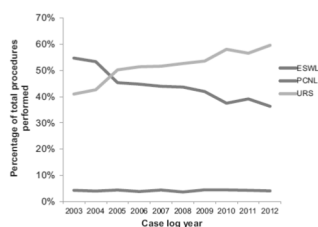


Figure 1. Change in stone treatment modality with time of all certifying urologists. ESWL, extracorporeal SWL.

Contemporary Surgical Trends in the Management of Upper Tract Calculi
Oberlin, Daniel T. et al.
The Journal of Urology, Volume 199, Issue 3, 880-884

SWL vs URS -- Ureteral

- SWL has less morbidity
 - Usually no stent
 - Ureteral injury not possible
- URS has a greater stone free rate per procedure
 - Laser lithotripsy is more effective than SWL
 - Greater morbidity

SWL vs URS

Cochrane 2012

- Seven RCT's (only 3 with adequate description of randomization)
- 1205 subjects
- RR stone free SWL 0.84 (CI 0.73-0.96)
- RR complications SWL 0.54 (CI 0.33-0.88)
- RR re-treatment SWL 6.18 (3.68-10.38)

Distal Ureteral Stones

AUA 2016

- URS
 - Semi-rigid URS has a 97-98% success rate
 - Stones > 10 mm median 95% success
- SWL
 - 70-75% median success for distal stones
- Unless patients refuse URS or cannot have URS, it should be considered first line for distal stones

Upper Ureteral Stones

Ng, J Urology 2009

- SWL in appropriate candidates
 - Size < 1 cm
 - Hounsfield Units < 800
 - Skin to stone distance < 9-10 cm
- Stone free rate (SFR) can be > 90% with good patient selection
 - SFR declines to 50-70% in candidates without good characteristics
- URS consistently offers 80-90% SFR

When Will URS Fail? (Tran 2017)

- Attempting URS on a ureteral stone carries a small risk of failure – 10-20%
- Change in serum creatinine and peri-ureteral inflammation can predict such failures
- Change in Cr > 0.3 mg/dL
 - Important for pre-operative counseling
 - Need to explain a second procedure may be required

EUST Score



TABLE 4. EMERGENCY URETERAL STONE TREATMENT SCORE

EUST score	Stone-free rate	p
0	20.6% (7/34)	<0.01 ^a
1	81.9% (77/94)	<0.01 ^b
2	99.2% (118/119)	—

^aComparison of stone-free rate for EUST score of 0 & 1 and 0 & 2.

^bComparison of stone-free rate for EUST score of 1 and 2.

EUST=Emergency Ureteral Stone Treatment.

Timothy Y. Tran, Natalia Hernandez Bustos, Avinash Kambadakone, Brian Eisner, and Gyan Pareek. Journal of Endourology. Sep 2017.

Renal Stones

- Renal anatomy
- Stone composition
- Stone size
 - Decision for PCNL
- Observation, URS, SWL, PCNL

Renal Stones

Steinberg/Hoenig, Smith's Endourology, 3rd ed
Pais, 2015

- Appx 20-25% need surgery over 3 years
- Lower pole stones are less likely to become symptomatic over 3 years of follow-up
 - 24% versus other locations 40%

Can observe many stones < 1 cm

Renal Stones < 2 cm

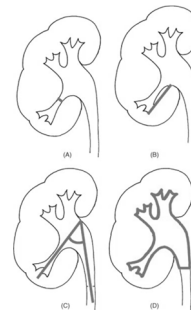
Steinberg/Hoenig, Smith's Endourology, 3rd ed
AUA Guidelines 2016

- SWL or URS
 - URS better SFR; more morbid
- Clearance of 80-90% feasible
- Lower pole
 - Clearance less than other locations (60-70%)
- PCNL almost 100% success but morbid

Lower Pole Stones 1-2 cm

- Lower Pole I Study
 - Randomized trial of SWL vs. PCNL
 - PCNL > 90% clearance and 6% 2nd procedure
 - SWL 25% clearance
- URS vs. PCNL (Pearle 2005)
 - URS 37% vs. PCNL 71% clearance
 - Unfavorable anatomy PCNL
 - Favorable anatomy consider URS

Lower Pole Anatomy



Extracorporeal Shock Wave Lithotripsy of Lower Calyx Calculi: How Much Is Treatment Outcome Influenced by the Anatomy of the Collecting System?
Danuser, Hansjörg et al.
European Urology, Volume 63, Issues 3, 526–546

Renal Stones > 2 cm = PCNL

- SWL and URS can be done
 - SFR are poor compared to PCNL
 - Residual fragments are the norm

URS > 2 cm Renal Stones

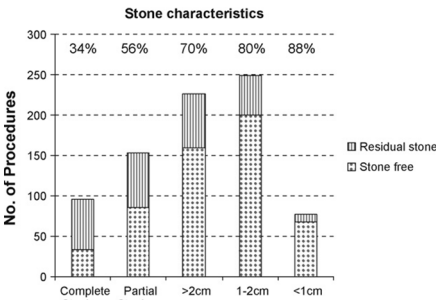
- Hyams et al 2010 – 120 patients
 - 86% single procedure
 - Stone free < 50%; < 4mm in 83%
- Breda et al 2008 – 15 pt's
 - All two stages (mean 2.3)
 - All but one stone free on US
- Hyams/Shah 2009 – 20 PCNL/19 URS
 - 89% vs 47% clearance (PCNL to URS)
 - Cost 1/3 for URS

URS for Larger Stones

- Distinct patient preference
- Substantial co-morbidity in the patient
 - Pulmonary disease
- Anatomic issues
 - Size
 - Positioning
 - Abnormal renal location/anatomy

PCNL: Stone Free Rates

European Urology 2012



Amirag, James N. et al. "Percutaneous nephrolithotomy in the United Kingdom: results of a prospective data registry." European urology 61 6 (2012): 1188-93.

S.T.O.N.E Nephrolithometry

Table 1. Summary of S.T.O.N.E. nephrolithometry scoring system.

Variable	1	2	3	4
Stone size (mm ²)	0-399	400-799	800-1599	≥1600
Tract length (mm)	≤100	>100		
Obstruction	None	Severe		
Calices (n)	1-2	3	Staghorn	stone
Essence (HU)	≤950	>950		

HU, Hounsfield units.

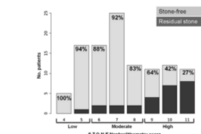


Figure 3. Number of patients stratified by low, moderate, and high nephrolithometry score risk groups.

Okhunov Z, Friedlander JI, George AK, Duty BD, Moreira DM, Srinivasan AK, Hillelsohn J, Smith AD, Okeke Z. Urology. 2013 Jun;81(6):1154-9.

S.T.O.N.E: High Score

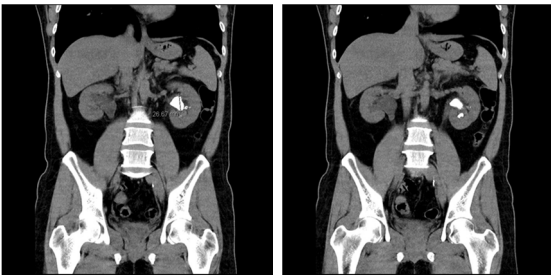


Image supplied by Peter L. Steinberg, MD

S.T.O.N.E: Low Score

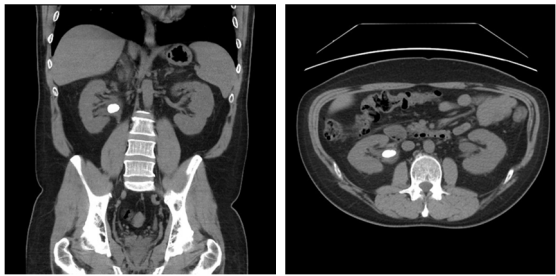


Image supplied by Peter L. Steinberg, MD

PCNL Outcomes

Table 2. Surgical outcome by large renal stone size

	20-30 Mm	31-40 Mm	41-60 Mm	p Value
No. pts	1,202	202	44	
Mean ± SD mins operative time (range)	71.3 ± 38.5 (5.0-70.0)	78.5 ± 40.3 (15.0-28.0)	90.8 ± 5.4 (30.0-10.0)	<0.001 (1-way ANOVA)
Mean ± SD days hospitalized (range)	3.7 ± 2.7 (0.0-26.0)	4.0 ± 3.4 (1.0-26.0)	4.0 ± 3.2 (1.0-19.0)	0.507 (1-way ANOVA)
% Stone free	90.0	83.3	84.1	0.015 (chi-square test)
% Postop Fever	8.4	7.3	17.9	0.038 (chi-square test)
% Blood transfusion	4.4	4.4	13.3	0.011 (chi-square test)

A Nephrolithometric Nomogram to Predict Treatment Success of Percutaneous Nephrolithotomy
Smith, Arthur et al.
The Journal of Urology, Volume 190, Issue 1, 149-156

Lap/Robotic Stone Management

- Concomitant stricture disease
- Concurrent lap/robotic procedure
- Failed URS, SWL, PCNL
- Aberrant anatomy
- Overall, these approaches are infrequently needed with today's techniques

Summary

- URS more effective than SWL
- SWL less morbid than URS
- Distal ureteral stones = URS
- Choose SWL candidates wisely
- PCNL for stones > 2 cm

Kidney Cancer: Active Surveillance

Adam S. Feldman, MD, MPH

Assistant Professor of Surgery
Director, Combined Harvard Urologic Oncology Fellowship
Director of Urologic Research
Department of Urology
Massachusetts General Hospital
Harvard Medical School, Boston MA



HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Disclosure



Reports no relationships with a commercial interest

Agenda



1. Small renal mass and RCC – epidemiology, pathology and staging
2. Treatment options for the small renal mass
3. Renal mass biopsy
4. Active treatment options – partial nephrectomy, nephrectomy, ablation
5. Active surveillance
6. Future directions – biomarkers

Epidemiology



In the U.S. in 2018 there are estimated to be:

- 65,340 new cases and 14,970 deaths from kidney cancer

Proportion of RCC found as incidental renal masses has increased from 10% in 1970's to now over 50%

Classic Triad (not commonly seen anymore)

- flank pain
- hematuria
- palpable mass

Male to Female ratio 2:1

Renal masses



85% of all renal tumors are RCC

Other malignant primary renal lesions in adults – TCC, sarcoma, lymphoma

Benign renal lesions – oncocytoma, angiomyolipoma, mixed epithelial stromal tumor (MEST), adenoma

RCC Risk Factors:

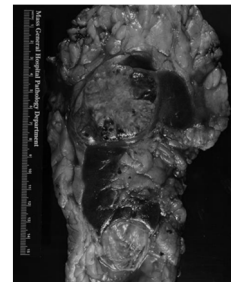
- Environmental: Smoking and Obesity
- HTN
- Family History in first degree relative
- Genetic Syndromes: von Hippel-Lindau (VHL), hereditary papillary RCC, Birt-Hogg-Dube Syndrome, Tuberous Sclerosis Complex, Hereditary Leiomyoma-RCC

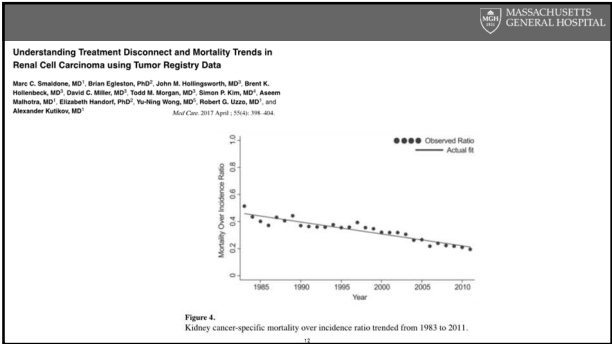
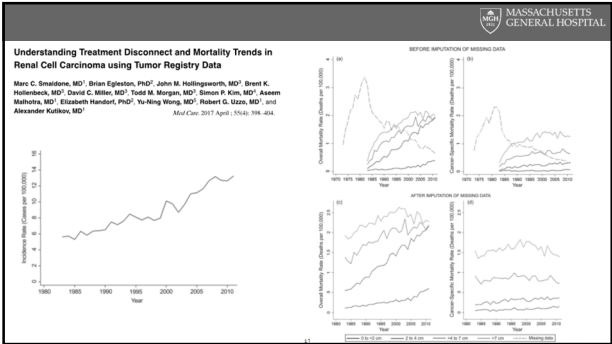
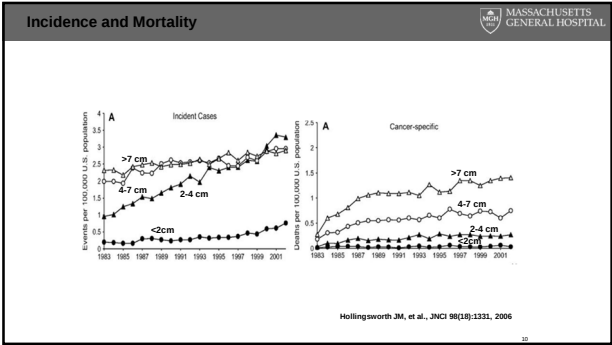
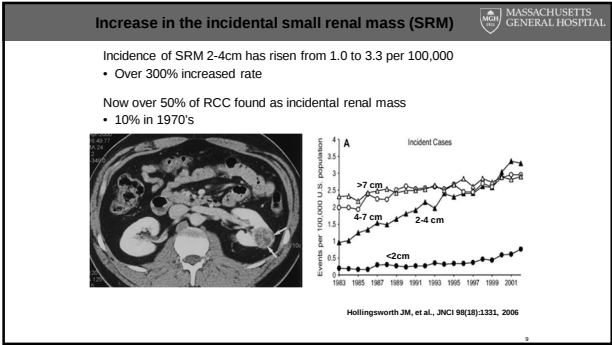
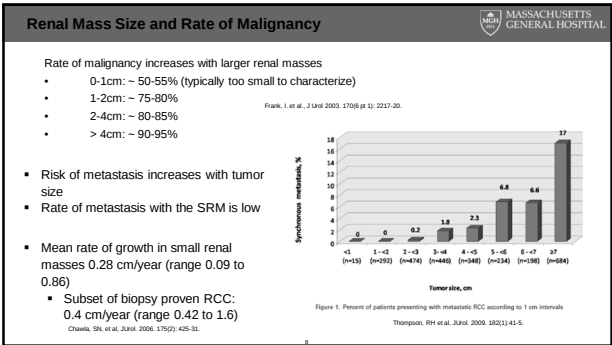
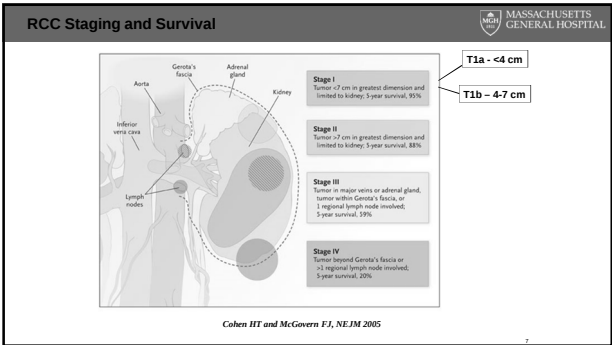
Pathology

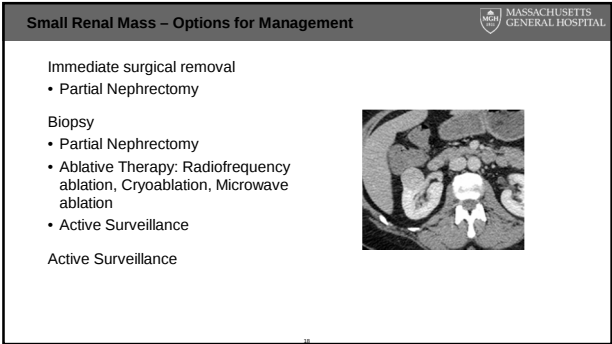
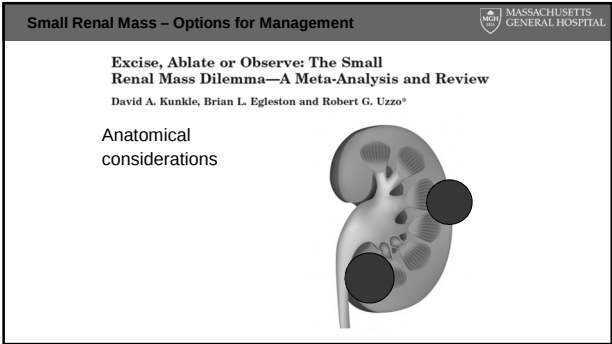
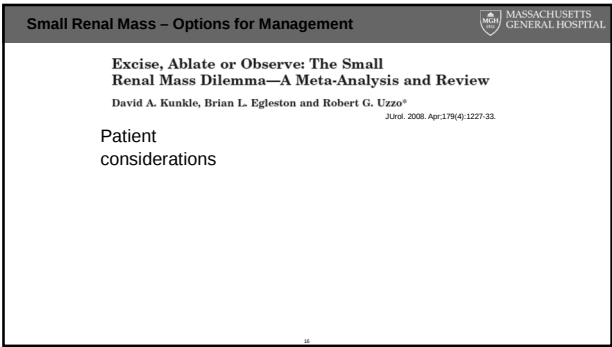
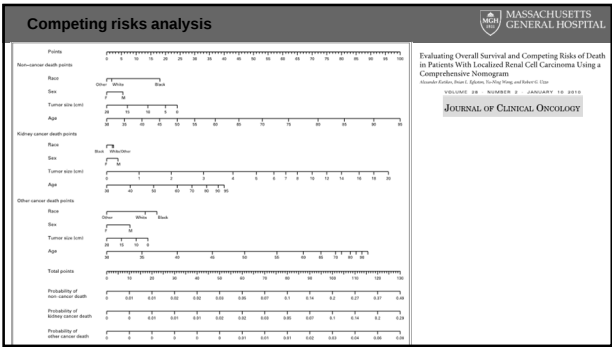
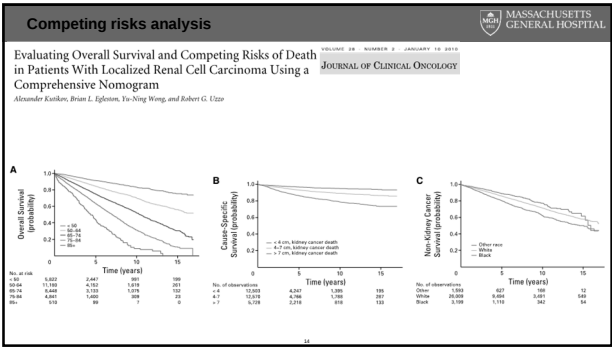
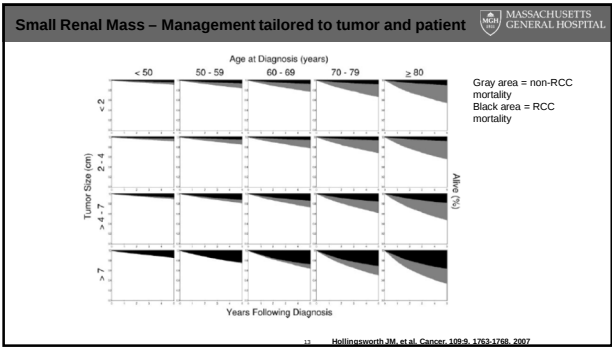


Pathologic Subtypes:

- Clear Cell (65%)
- Papillary (15%)
 - Type I – low grade tumors
 - Type II – higher propensity for metastasis
- Chromophobe (10%) – less aggressive
- Collecting Duct Carcinoma – poorer prognosis
- Xp11 translocation RCC
 - Children – indolent
 - Young adults – more aggressive
- Clear cell papillary
- Hybrid oncocytic chromophobe
- All subtypes can express sarcomatoid features, which suggest a poor prognosis

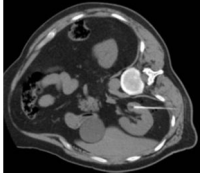




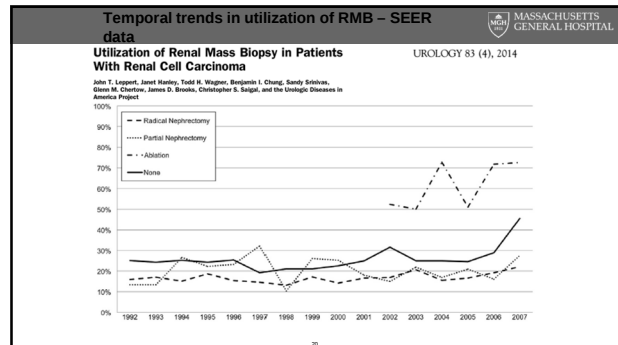


Renal Mass Biopsy

- Rationale –
 - May prevent nephrectomy or partial nephrectomy for benign disease
 - May distinguish RCC from other malignancy
- Survey of 190 members of Endourological Society:
 - 73% report "never" or "rarely" performing biopsies
 - Cite lack of influence on clinical management & risk of false negative



Barwari K, de la Rosette JJ, Laguna MP. J Endourol. 2012 Feb.



Guidelines

AUA Guidelines:

- RMB should be considered when a mass is suspected to be hematologic, metastatic, infectious, or inflammatory and after a thorough discussion of the risks and benefits

NCCN Guidelines:

- RMB may be considered in small masses to confirm malignancy and help guide decisions regarding active surveillance and the various ablative techniques

EAU Guidelines:

- RMB is reasonable prior to either surveillance or ablation but report only a grade C level of evidence

Predictors of a diagnostic biopsy

Table 4. Univariable and multivariable analysis of factors associated with a diagnostic biopsy at the time of the initial renal tumor biopsy (n = 529)

Variables	Univariate			Multivariate ^a		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Patients characteristics						
Age, yr (per 1-yr increase)	1.02	1.00-1.04	0.04	1.02	0.99-1.04	0.16
Gender (female vs male)	1.20	0.66-2.17	0.55			
BMI, kg/m ² (per 1 kg/m ² increase)	1.04	0.96-1.12	0.38			
ASA score (2 vs 1)	0.71	0.38-1.30	0.26			
Lesion characteristics						
Kidney biopsy (right vs left)	1.05	0.60-1.86	0.88			
Lesion location						
Middle vs lower pole	1.51	0.77-2.97	0.23			
Biopsy location						
Upper vs lower	1.38	0.69-2.65	0.46	1.71	1.17-2.50	0.006
Tumor size, cm, per 1-cm increase	1.58	1.12-2.08	<0.001	1.51	1.17-2.00	<0.001
Final biopsy grade, per 1-point increase	3.15	1.75-5.70	<0.001	2.51	1.56-4.44	<0.001
Prevalence characteristics						
Previous no. of biopsies performed per provider at the time of biopsy (per 1 biopsy increase)	1.00	0.98-1.01	0.48			
Type of imaging used, ultrasound vs CT	2.00	1.08-3.70	0.03	1.71	0.88-3.31	0.11
Year of biopsy, per 1-yr increase	1.08	0.97-1.20	0.16	1.08	0.96-1.22	0.21

ASA = American Society of Anesthesiologists (classification); BMI = body mass index; CI = confidence interval; CT = computed tomography.

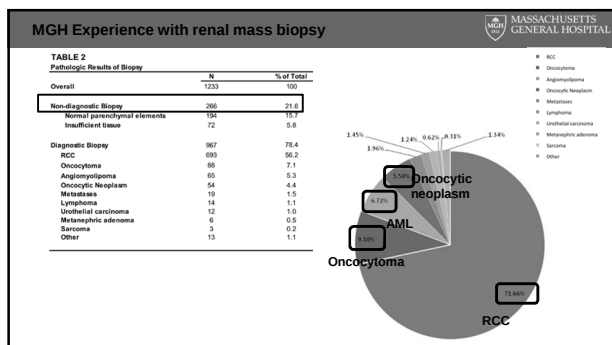
^a Hosmer-Lemeshow goodness-of-fit test: 0.68.

^b C statistic: 0.72.

Renal Tumor Biopsy for Small Renal Masses: A Single-center 13-year Experience

Patrick O. Richard¹, Michael A. Jewett², Justin R. Bhatt³, John R. Kuchars⁴, Andrew J. Evans⁵, Alexandre R. Zetter⁶, Thomas Hermann⁷, Tristan Javer⁸, Antonio Fardip⁹

¹Department of Urology, ²Department of Urology, ³Department of Urology, ⁴Department of Urology, ⁵Department of Urology, ⁶Department of Urology, ⁷Department of Urology, ⁸Department of Urology, ⁹Department of Urology



Solid vs. Cystic masses

Characteristics of Solid vs. Cystic Lesions

	Solid lesions		Cystic lesions		P Value
	N	%	N	%	
Total	1020	100	213	100	
Non-diagnostic Biopsy	129	12.6	137	64.3	< 0.001
Diagnostic Biopsy	891	87.4	76	35.7	< 0.001
RCC	630	70.7	63	82.9	
Oncocytoma	67	8.0	7	9.0	
Angiomyolipoma	61	6.8	4	5.3	
Oncocytic Neoplasm	54	6.1	0	0.0	
Metastases	16	1.8	3	3.9	
Urothelial carcinoma	11	1.2	1	1.3	
Other	32	3.6	4	5.3	

% of diagnostic biopsies are italicized

Avoid RMB in cystic lesions unless considering ablation or majority solid component

- Can deflate cyst and make follow up imaging challenging or complicate partial nephrectomy

Smaller lesions have a higher non-diagnostic rate and lower risk of malignancy



Histology	< 1.5 cm		1.5 - 4 cm		4.1 - 7 cm		> 7 cm	
	n	%	n	%	n	%	n	%
Total	100	9.8	711	69.7	107	76.4	42	5.1
Diagnostic Biopsy	71	71.6	635	89.3	148	88.6	37	88.1
BCG	45	63.4	442	69.6	112	76.7	31	83.8
Oncocytoma	5	6.8	71	11.2	8	5.4	1	2.7
Angiomyolipoma	11	10.5	44	6.9	4	2.7	2	6.4
Oncocytic Neoplasm	5	7.0	41	6.5	7	4.7	1	2.7
Metastases	1	1.4	11	1.7	3	2.0	1	2.7
Unidentified carcinoma	0	0.0	6	0.9	5	3.4	0	0.0
Other	2	2.8	20	3.1	9	6.1	1	2.7
Non-diagnostic Biopsy	29	29.0	76	10.7	19	11.4	5	11.9

total n = 5,001

% of diagnostic biopsies are italicised

RCC Histologic Characteristics			
	N	% of Total	
Overall	693	100	
Histologic Subtype			
Clear Cell	397	57.3	Subtype reported 83%
Papillary	140	20.2	
Chromophobe	33	4.8	
Sarcomatoid	3	0.4	
Translocation	2	0.3	
Not reported	118	17.0	
Histologic Grade			
Low	206	29.7	Grade reported 35%
High	36	5.2	
Not reported	451	65.1	

Systematic reviews

Study	Sensitivity (%)	Specificity (%)
Lavrenco Marconi ¹ , Javed Dohatabi ² , Thomas E Lam ³ , Schelen Hoffmann ⁴ , Hani Sereeni ⁵ , John Nouri ⁶ , Axel Brix ⁷ , Martin Bruchardt ⁸ , Steven E Campbell ⁹ , Miles Horan A Kuczyk ¹⁰ , Axel S Muehlebach ¹¹ , Peter F A Mulders ¹² , Thomas Porzik ¹³ , Michael Stuckert ¹⁴ , Bojan Ljumbegjic ¹⁵ , Alessandro Volpe ¹⁶	99.1%	99.7%

■ Overall sensitivity – 99.1%; specificity – 99.7%

RMB is a safe procedure, but not absolutely benign

RESEARCH IN PROGRESS

Renal Tumor Biopsy for Small Renal Masses: A Single-center 13-year Experience

Patrick O. Richard, Michael A.S. Jewett*, Jaimin R. Bhatt*, John R. Kichura*, Andrew J. Evans*, Alexandre R. Zietza**, Thomas Hermanns*, Brittan Jover*, Antonio Facelli**

RESEARCH IN PROGRESS

Table 5 – Adverse events reported following renal tumor biopsies (n = 509 patients)

Type	n (%)
Peritoneal hematoma	24 (4.7)
Conservative	23 (95.8)
Percutaneous angiomebolization	1 (4.2)
Skin hematoma	1 (0.2)
Venous bleeding through coaxial sheath	12 (2.4)
Self-limited	5 (41.7)
Hemostatic agents used	7 (58.3)
Self-limited gross hematuria	5 (1.0)
Nausea/Vomiting	1 (0.2)
Persistent pain	3 (0.6)
Dizziness	2 (0.4)

■ No cases of needle tract seeding

RESEARCH IN PROGRESS

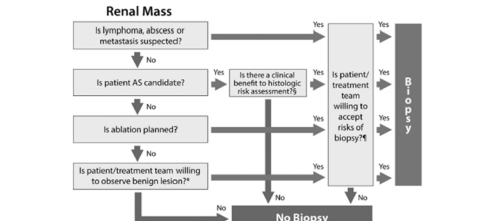
RMB is a safe procedure, but not absolutely benign

Of 1233 Biopsies at MGH:

- 8 Complications requiring admission –
 - Retroperitoneal bleed → acute cardiac event → death
 - Acute HTN → stroke
 - Gross hematuria and renal colic
 - RP bleed/subcapsular hematoma with pain
 - Flank pain, shortness of breath
 - Compression neuropathy from positioning
 - 2 Post-procedure nausea
- **There were no cases of needle tract seeding**

Algorithm for selection for renal mass biopsy

 MASSACHUSETTS GENERAL HOSPITAL



```

    graph TD
      Q1[Is lymphoma, abscess or metastasis suspected?] -- Yes --> B[Biopsy]
      Q1 -- No --> Q2[Is patient AS candidate?]
      Q2 -- Yes --> Q3[Is there a clinical benefit to histologic risk assessment?]
      Q2 -- No --> Q4[Is ablation planned?]
      Q3 -- Yes --> Q5[Is patient/treatment team willing to accept risks of biopsy?]
      Q3 -- No --> NB[No Biopsy]
      Q4 -- Yes --> Q5
      Q4 -- No --> NB
      Q5 -- Yes --> B
      Q5 -- No --> NB
      Q6[Is patient/treatment team willing to observe benign lesion?] -- No --> NB
      Q6 -- Yes --> NB
  
```

Renal Mass

Is lymphoma, abscess or metastasis suspected?

Yes → Biopsy

No → Is patient AS candidate?

Is patient AS candidate?

Yes → Is there a clinical benefit to histologic risk assessment?

No → Is ablation planned?

Is there a clinical benefit to histologic risk assessment?

Yes → Is patient/treatment team willing to accept risks of biopsy?

No → No Biopsy

Is ablation planned?

Yes → Is patient/treatment team willing to accept risks of biopsy?

No → No Biopsy

Is patient/treatment team willing to accept risks of biopsy?

Yes → Biopsy

No → No Biopsy

Is patient/treatment team willing to observe benign lesion?

No → No Biopsy

Yes → No Biopsy

Biopsy

No Biopsy

Renal Mass Biopsy: Always, Sometimes, or Never?

EUROPEAN UROLOGY 70 (2016) 403–406

Alexander Kutikov^{a,c}, Marc C. Smaldone^a, Robert G. Uzzo^a, Miki Hafliger^a,

Renal Mass Biopsy – Indications

Renal mass considered for ablative therapy

Significant surgical comorbidity/risk, advanced age

Multiple suspicious renal masses

Solitary kidney or significant renal insufficiency

Known extra-renal malignancy and concern for metastasis

Concern for abcess/infectious cause

Select genetic syndrome (eg. TSC) or suspicion of genetic syndrome

Surgically unresectable disease

But...RMB is not absolutely indicated for every renal mass!

Renal Mass Biopsy – who can avoid a biopsy?

Patients with cystic lesions

Patients who have a limited life expectancy in whom surveillance would be chosen in spite of the biopsy result

Younger healthy patients who have a very high rate of surgical intervention after the biopsy and who wish to avoid the need for indefinite follow up imaging

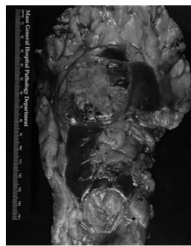
Goals of treatment

Oncologic control

- Local control
- Prevention of distant metastases

Avoid complications and additional procedures

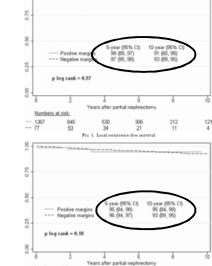
Preserve renal function



Partial nephrectomy – Oncologic outcomes

TABLE 1. Clinical and pathological characteristics of 1,344 patients undergoing 1,395 partial nephrectomies

	Male	Female
No. test	619	771
Age at surgery		
Median (IQR)	63 (54-71)	64 (55-66)
Range	38-86	58-82
No. gender (n)		
Male	179 (29)	257 (33)
Female	440 (71)	514 (67)
No. side (n)		
Right	291 (47)	392 (51)
Left	328 (53)	379 (49)
No. tumor in solitary kidney		
Yes	59 (10)	76 (10)
Max tumor diameter (cm)		
Mean (SD)	3.5 (1.9)	3.1 (1.4)
Median (IQR)	3.0 (2.4-3.6)	2.6 (2.0-3.3)
Range	0.5-10.0	0.5-10.0
Pathologic stage		
T1a	448 (72)	567 (73)
T1b	139 (22)	96 (12)
T2	16 (3)	11 (1)
T3	16 (3)	11 (1)
T4	6 (1)	6 (1)
Pathologic stage (n)		
Pathologic stage	406 (66)	507 (66)
Pathologic stage	32 (5)	64 (8)
Pathologic stage	402 (66)	478 (62)
Pathologic stage	173 (28)	148 (19)
Pathologic stage	173 (28)	92 (12)
Pathologic stage	38 (6)	43 (6)
Pathologic stage	4 (1)	11 (1)



Yossepowich et al. JUrol. 179. 2008

RFA Oncologic control - What are the data?

Long-Term Oncologic Outcomes After Radiofrequency Ablation for T1 Renal Cell Carcinoma

Sarah P. Rutka^{a,y}, Adam S. Feldman^{a,y}, W. Scott McDougall^{a,*}, Francis J. McGovern^a, Peter Mueller^b, Debra A. Gervais^b

*Department of Urology, Massachusetts General Hospital, Boston, MA, USA; †Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

185 patients

All biopsy-proven sporadic BCC

24 retreated for residual disease

12 local recurrences

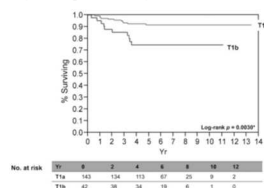


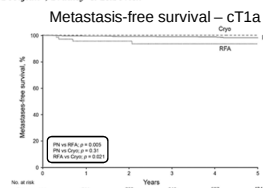
Fig. 1 - Disease-free survival (ie, no recurrence, no metastases): Disease status at last follow-up.

PN vs. Ablation

Comparison of Partial Nephrectomy and Percutaneous Ablation for cT1 Renal Masses

EUROPEAN UROLOGY XXX (2014)

R. Houston Thompson^{a,c}, Tom Atwell^b, Grant Schmit^b, Christine M. Lohse^c, A. Nicholas Kurup^b, Adam Weisbrod^b, Sarah P. Psutka^a, Suzanne B. Stewart^a, Matthew R. Callstrom^b, John C. Chevillat^a, Stephen A. Boorjian^a, Bradley C. Leibovich^a



Small Renal Mass – Options for Management

- Immediate surgical removal
 - Partial Nephrectomy
- Biopsy
 - Partial Nephrectomy
- Ablative Therapy: Radiofrequency ablation, Cryoablation, Microwave ablation
- Active Surveillance

Active Surveillance



Certainly complications occur after surgery

Objective Measures of Renal Mass Anatomic Complexity Predict Rates of Major Complications Following Partial Nephrectomy

Jay Srinivasan¹, Marc C. Smalldone², Kevin J. Tsi³, Daniel J. Quinlan⁴, Tianyu Li⁵, Alexander Kikina⁶, Raulin Vitorio⁷, David Y. Chen⁸, Rainer G. Gremberg⁹, Robert G. Uzzo¹⁰

¹Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ²Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ³Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ⁴Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ⁵Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ⁶Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ⁷Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ⁸Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ⁹Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ¹⁰Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Table 1. Complication rates reported by patient

	Low complexity group (N=10)	Medium complexity group (N=10)	High complexity group (N=10)	P value
Major complications (Clavien ≥3)	0 (0%)	0 (0%)	0 (0%)	0.99
Minor complications (Clavien 1-2)	0 (0%)	0 (0%)	0 (0%)	0.99
Major complications (Clavien ≥3)	0 (0%)	0 (0%)	0 (0%)	0.99
Minor complications (Clavien 1-2)	0 (0%)	0 (0%)	0 (0%)	0.99

Table 2. Incidence of individual complication by Clavien-Borde classification system type within 30 d of surgery categorized by organ system

	Low complexity group (N=10)	Medium complexity group (N=10)	High complexity group (N=10)	P value
Clavien-Borde	0 (0%)	0 (0%)	0 (0%)	0.99
Clavien-Borde	0 (0%)	0 (0%)	0 (0%)	0.99
Clavien-Borde	0 (0%)	0 (0%)	0 (0%)	0.99
Clavien-Borde	0 (0%)	0 (0%)	0 (0%)	0.99

RFA and Cryo Complications

Percutaneous Ablation of Renal Masses Measuring 3.0 cm and Smaller: Comparative Local Control and Complications After Radiofrequency Ablation and Cryoablation

Thomas B. Kneib¹, David B. Kneib², Stephen A. Kneib³, A. Nicholas Kneib⁴, Robert A. Kneib⁵, George A. Kneib⁶, Robert A. Kneib⁷, David E. Kneib⁸, Robert A. Kneib⁹, Robert A. Kneib¹⁰

AJR 200, February 2013

TABLE 1. Major Complications of Radiofrequency Ablation (RFA) and Cryoablation

Procedure/Complication	No. (%) of Complications
RFA (n=22)	
Major complications	0 (0%)
Minor complications	0 (0%)
Clavien-Borde	0 (0%)
Cryo (n=18)	
Major complications	0 (0%)
Minor complications	0 (0%)
Clavien-Borde	0 (0%)

- 232 percutaneous RFA
- 176 percutaneous Cryo
- Major complications:
 - RFA - 4.3%
 - Cryo - 4.5%

MGH RFA Cohort - Complications

374 RFAs – 1998 – 2013

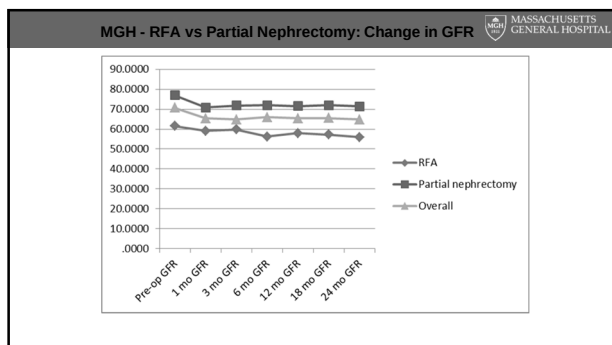
Clavien grade ≥3 complications = 19 (5.1%)

- Collecting system injury 2.4%
- Bowel injury 0.8%
- Sepsis 0.3%

Predictors for high-grade complications:

- Tumor size >3 cm
- Endophytic tumor
- Medial location of tumor
- High RENAL nephrometry score (≥10)

Anecdotal, the ureteral and collecting system injuries seen after RFA may be more difficult to manage and resolve than after PN



Active Surveillance

Renal Mass and Localized Renal Cancer: AUA Guideline

Steven Campbell, Robert G. Uzzo, Mohamed E. Altai, Eric B. Bass, Jeffrey A. Caddebo, Anthony Chang, Peter E. Clark, Brian J. Davis, Brian H. Denvesh, Leo Giambardino, Debra A. Gervais, Susie L. Hu, Brian R. Lane, Bradley C. Leibovich and Philip M. Pierorazio

THE JOURNAL OF UROLOGY® Vol. 188, 520-526, September 2017

Active Surveillance (AS)

- For patients with renal masses suspicious for cancer, especially those <3cm, AS is an option for initial management.
- Prioritize AS/Expectant Management when the anticipated risk of intervention or competing risks of death outweigh the potential oncologic benefits of active treatment.
- When the risk/benefit analysis for treatment is equivocal and the patient prefers AS, physicians should repeat imaging in 3-6 months to assess for interval growth and may consider RMB for additional risk stratification.
- When the oncologic benefits of intervention outweigh the risks of treatment and competing risks of death, physicians should recommend active treatment. In this setting, AS may be pursued only if the patient understands and is willing to accept the associated oncologic risk.

Factors Favoring AS/Expectant Management

Patient-related	Tumor-related
Elderly	Tumor size <3cm
Life expectancy <5 years	Tumor growth <5mm/year
High comorbidities	Non-inflamatory
Excessive perioperative risk	Low complexity
Frailty (poor functional status)	Favorable histology
Patient preference for AS	
Marginal renal function	

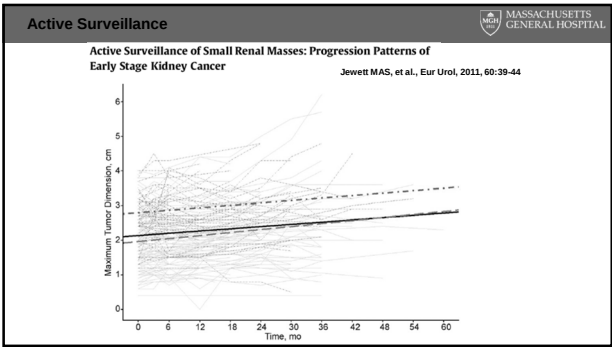
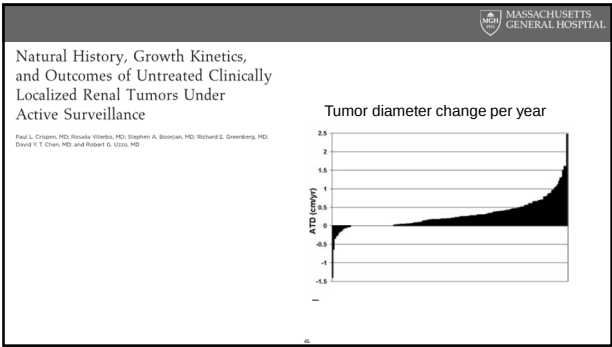
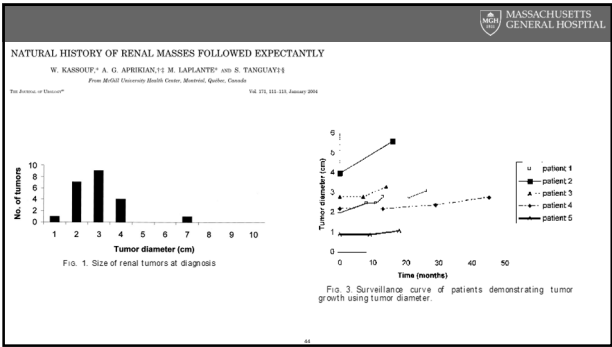
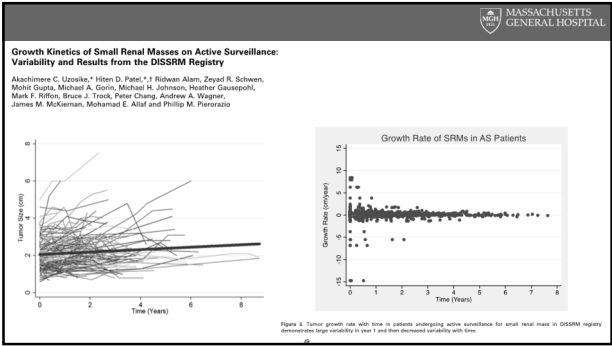
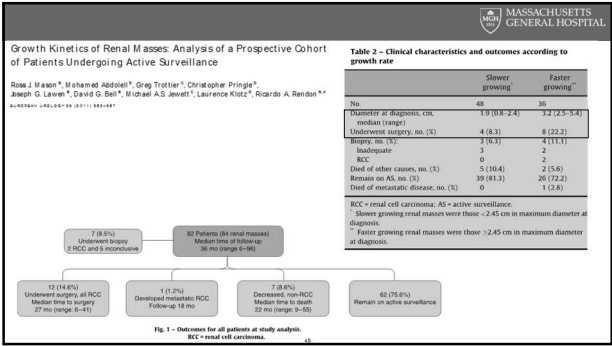


Table 1. Nonredundant contemporary series of active surveillance

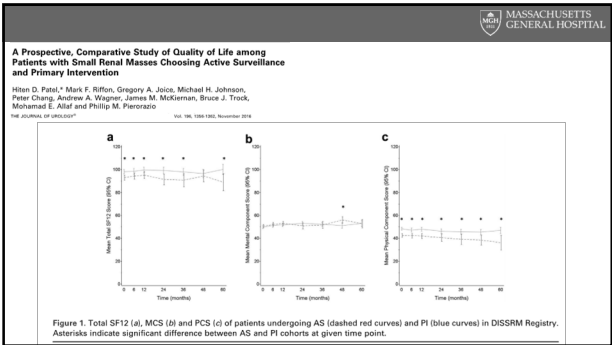
AS Series	Patients/Lesions (n)	Mean Tumor Size (cm)	Mean Growth Rate (cm/yr)	Mean Follow-Up (mo)	Delayed Surgery (n)	Progression to Metastasis (n)	Deaths (n)
Bosniak et al., ¹⁹ 1995	37/40	1.73	0.36	39	26 (65)	0	3* (8)
Kassouf et al., ²⁰ 2004	24/26	3.27	0.09	32	4 (17)	0	0
Vogge et al., ²¹ 2004	29/32	2.48	0.1	27.9	8 (27)	0	2* (6.9)
Wells et al., ¹⁶ 2004	29/29	1.83	0.12	32	6 (21)	0	2* (6.9)
Lamb et al., ²⁴ 2004	36/36	7.2	0.39	24	0	1 (2.8)	13* (36)
Chamie et al., ²² 2006	49/61	2.6	0.2	36	20	1 (2)	NA
Kouba et al., ²³ 2007	43/46	2.92	0.7	35.8	13 (30)	0	4* (10)
Abou Youssef et al., ⁶ 2007	35/44	2.2	0.21	47.6	8 (23)	2 (5.7)	9* (26)
Aborassaby et al., ²⁵ 2008	110/110	2.5	0.26	24	4 (4)	2 (1.8)	34* (31)
Crispen et al., ⁸ 2009	154/173	2.45	0.28	31	68 (44)	2 (1.8)	NA
Rosales et al., ¹⁷ 2010	212/223	2.8	0.34	35	11 (5.1)	4 (1.9)	1 (0.5)
Total	758/820	2.9	0.27	33.1	157 (20.7)	12 (1.6)	NA

AS, active surveillance; NA, not available.
* Nonspecific.

UROLOGY 76 (3), 2010







Active Surveillance

Small Renal Masses Progressing to Metastases Under Active Surveillance

A Systematic Review and Pooled Analysis Smaildone MC, et al, Cancer, 2012, 118:997-1006

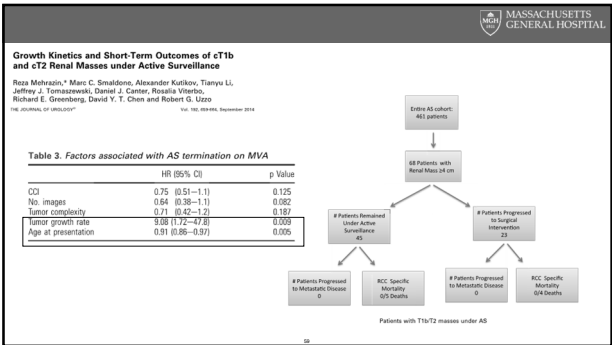
Table 3. Comparison of Clinical and Cross-Sectional Imaging Characteristics in Patients who Did Not Progress to Metastasis (Pooled Cohort Series Data) and Patients who Demonstrated Evidence of Progression (Case Series Data) During Periods of Observation

Characteristic	Nonprogressors		Progressors		P
	No.	Mean±SD; Median (Range)	No.	Mean±SD; Median (Range)	
Age, y	250	66.6±12.3; 69 (55-88)	9	75.1±9.1; 70.0 (64.0-84.0)	.03
Initial MTD, cm	281	2.5±1.3; 2.0 (0.5-12.0)	16	4.3±2.1; 3.1 (2.0-8.8)	<.001
Initial ETV, cm ³	281	15.1±60.3; 4.0 (0.004-602.7)	16	60.3±100.0; 15.2 (4.3-363.0)	<.001
Final MTD, cm	249	3.5±1.6; 2.7 (0.9-15.0)	14	5.9±2.1; 5.9 (3.1-10.7)	<.001
Final ETV, cm ³	281	20.0±108.0; 10.0 (0.3-1765.9)	14	152.1±170.9; 97.0 (15.4-603.0)	<.001
Linear growth rate, cm/y	249	0.4 (0.3-0.5) (-1.4-2.47)	13	0.8 (0.7-0.8) (0.1-1.27)	<.001
Volume growth rate, cm ³ /y	281	6.2±37.5; 1.6 (-20.4-60.7)	14	27.1±34.9; 18.1 (4.0-84.4)	<.001
Time under AS, mo	281	33.3±22.6; 27.0 (0.3-106.0)	17	40.2±31.2; 29.0 (0.0-132.0)	.47

Abbreviations: AS, active surveillance; ETV, estimated tumor volume; MTD, maximum linear tumor dimension; SD, standard deviation.

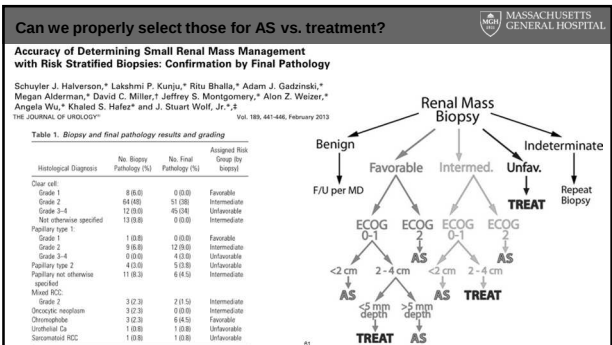
Tumor size and growth rate correlate with progression vs. non-progression

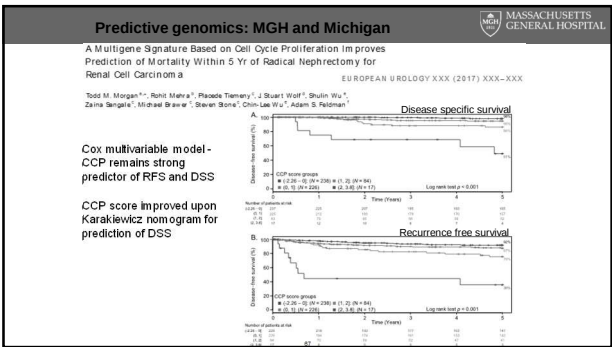
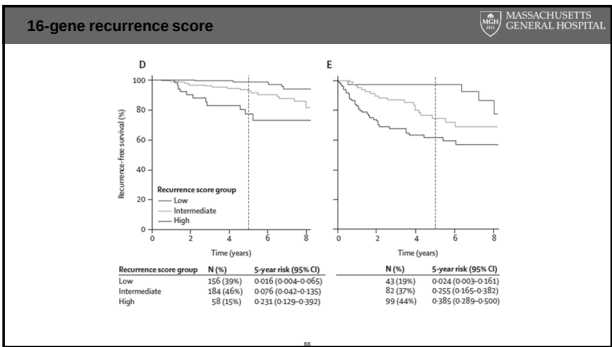
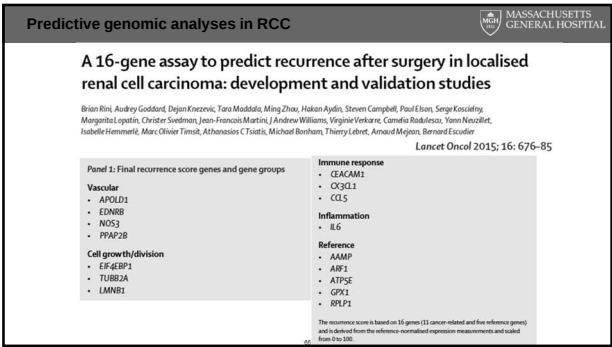
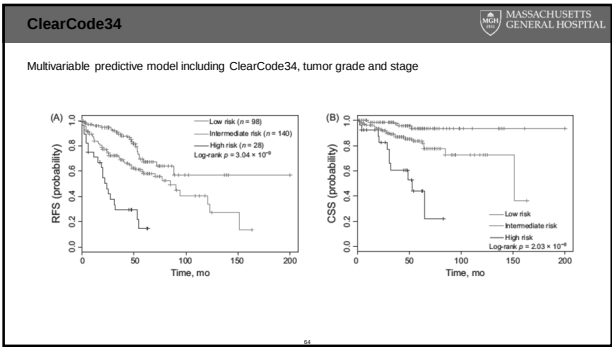
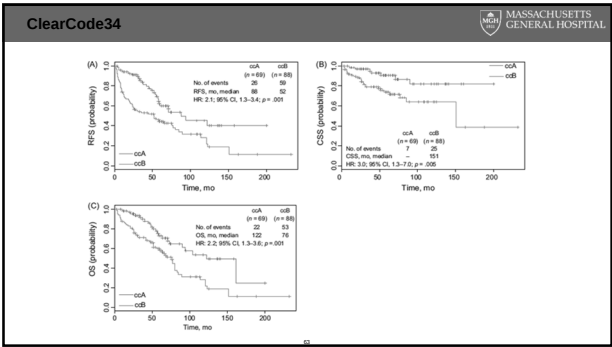
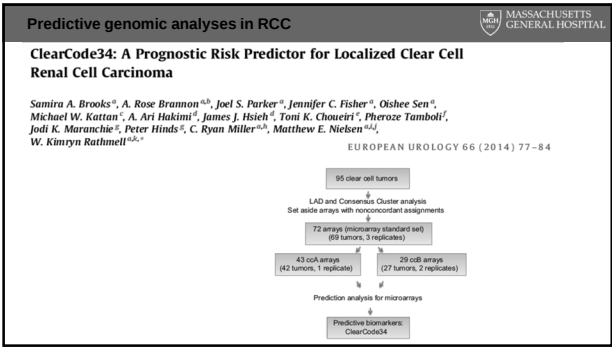
- Larger tumors?**
- Active Surveillance for Larger (cT1bN0M0 and cT2N0M0) Renal Cortical Neoplasms**
- Adam C. Morse, George Harman, Natan Badani, Manu Gupta, Mitchell C. Benson, James M. McKiernan, and Jaime Landman
- Urology 76: 622-623, 2010.
- 36 patients with 42 renal masses ≥ 4 cm
 - Mean tumor size 7.13cm (range 4-13.7)
 - Mean growth rate 0.57cm/year (range 0-5.9cm)
 - Mean follow up 36 months
 - 5 patients (13.8%) proceeded to treatment
 - Two patients (5.6%) developed metastatic disease

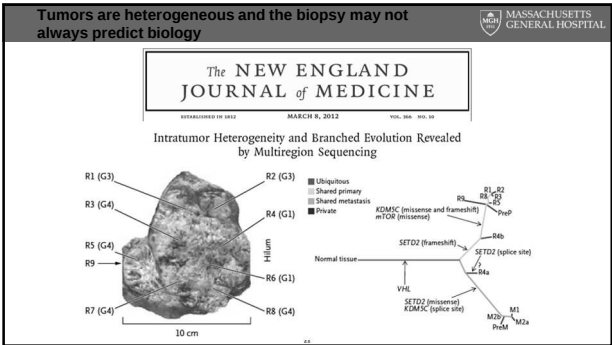


Summary of Guidelines

Guideline	Criteria for AS	Surveillance
ASCO, 2017 ²	- Initial management option for patients who have significant co-morbidities and limited life expectancy - Absolute indication: high-risk for general anesthesia or life expectancy < 5 years - Relative indication: significant risk of ESRD if treated, SRM (< 1 cm), or life expectancy < 10 years	- CXR and axial abdominal imaging (or US) every 3 months for 1 year, twice in year 2-3, and yearly thereafter - Modify surveillance based on growth kinetics
AUA, 2017 ²⁷	- Elderly, life expectancy < 5 yrs, high co-morbidities, excessive perioperative risk, poor functional status, marginal renal function, patient preference to avoid treatment risk - Tumor size < 3 cm, tumor growth < 5mm/year, non-infiltrative on imaging, low complexity, favorable histology (if RMB performed), Bosniak 3 or 4 complex cyst, especially if < 2 cm	- Initial imaging after 3-6 months - Decision as to the frequency and imaging modality must be customized and informed by robust communication focusing on goals, risks and triggers for intervention
NCCN, 2017 ^{24a}	Decreased life expectancy or extensive co-morbidities that would place them at excessive risk for more invasive intervention	- Abdominal CT or MRI within 6 months of surveillance initiation and yearly thereafter - CXR or CT annually if RMB positive for RCC - Bone scan/pelvic/head imaging if clinically indicated - CT, MRI or US at 3 and 6 months, then every 6 months until 3 year, and then annually
EAU, 2015 ⁵¹	Elderly and/or co-morbid patients with SRM and decreased life expectancy	







Management?

MASSACHUSETTS GENERAL HOSPITAL

- Risk of mets – rare!
- Risk of surveillance as initial strategy – low

Management?

MASSACHUSETTS GENERAL HOSPITAL

70 yo man with diabetes and HTN

- Chance of avoiding surgery up to 30%

22

Management?

MASSACHUSETTS GENERAL HOSPITAL

45 yo healthy M with 2.7 cm enhancing solid renal mass seen incidentally on CT scan done for abdominal pain. CT report states “amenable to percutaneous biopsy.”

23

Conclusions

MASSACHUSETTS GENERAL HOSPITAL

Active Surveillance is an accepted management strategy for small renal masses in appropriately selected patients at greater surgical risk

Patients should be monitored carefully for change over time and growth rate, and should be transitioned to treatment if needed

Future biomarker and imaging development will hopefully improve our selection of patients for active surveillance

24

Thank you!

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Kidney Cancer: Open Surgical Management

MD Anderson
Cancer Center

Making Cancer History™

Christopher G. Wood, M. D., FACS
Douglas E. Johnson, M. D. Endowed Professorship in Urology
Professor and Deputy Chairman, Department of Urology
The University of Texas MD Anderson Cancer Center

Disclosures

- Research Grants: Argos Therapeutics, Pfizer, Bristol Myers Squibb
- Advisory Role: Merck
- Board Membership: Kidney Cancer Association
- Honoraria: Merck, Argos Therapeutics

Open Surgical Management in Kidney Cancer

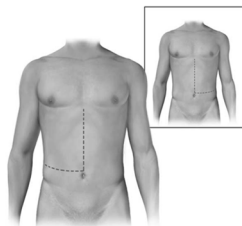
- There are no absolute indications for open surgical management in Kidney Cancer
- Anything done through open surgical approaches has been replicated laparoscopically or with robotic assisted laparoscopy
 - Whether that is good or bad is in the eye of the beholder....
- Relative Indications for Open Surgery
 - Venous involvement
 - Adjacent organ involvement
 - Need for a meticulous and thorough lymph node dissection
 - Large tumors
 - Complex partial nephrectomies with multiple tumors or complex reconstruction

Open Surgical Management in Kidney Cancer

- The most important tenet of oncologic surgery is oncologic control
- Approach is secondary at most to that tenet
- Having a minimally invasive, cosmetically appealing surgery and not be cured of your cancer serves no one.
- Don't apologize for having open surgery in your repertoire.
 - Choose the approach that most assures it will control the cancer, preserve and maximize renal function, and minimize morbidity to the patient
 - I worry that open surgical techniques may become a "lost art".
 - It is important that we carry ourselves as physicians and surgeons, not technicians.

Incisions

- Midline
- Flank
 - 11th rib
 - No resection of the rib
- Modified Makuuchi
 - Adjacent organ invasion
 - Large upper pole tumors
- Chevron
- Subcostal



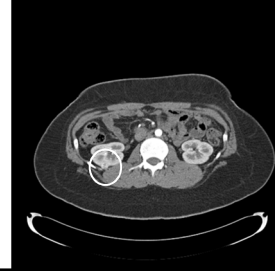
Chang SB et al, Arch Surg, 2010

The Role of Lymph Node Dissection in the Management of Renal Cell Carcinoma

Relevant Clinical Questions Regarding Lymph Node Dissection for Renal Cell Carcinoma

- Who should have one? (or when can it be avoided?)
 - Tumor size
 - Stage
 - Histology
 - Lymph node size on imaging or intraoperative assessment
- What is an adequate lymph node dissection?
 - Hilar
 - Clear off ipsilateral vessel (from hilum?, crus? to bifurcation)
 - Ipsilateral and interaortocaval
 - Full bilateral
- Can an adequate lymph node dissection be performed minimally invasively? (laparoscopic or robotic assisted)

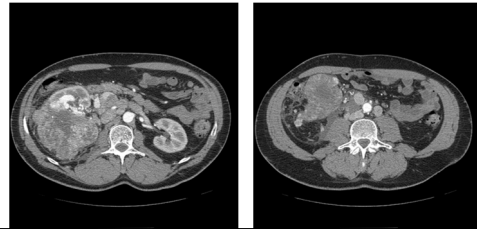
29 y/o HF with abdominal pain



Can we all agree that this patient is unlikely to benefit from LND?

- Arguably may not even need immediate treatment for primary tumor
- Biopsy may guide further therapy
- Potential Exceptions
 - HLRCC
 - Papillary type II
 - Xp11 Translocation

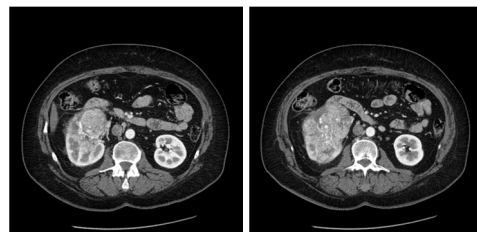
57 y/o WM with gross hematuria



Can we all agree that we would be likely to perform an aggressive LND in the absence of metastatic disease?

- Benefit unclear
- Evidence level 3 at best
- Role of neoadjuvant/adjuvant therapy unknown
- Knowledge of histology may play a role
- Best chance at “cure” if cure is possible

55 y/o WF presents with abdominal pain



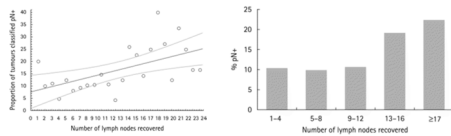
65 y/o HM with gross hematuria



Will these patients benefit from LND?

- “Level 1 evidence” says no
- Technique of resection may remove ipsilateral nodes as “collateral damage”
- Staging may be relevant in predicting prognosis and stratification for adjuvant trials
- Clinically relevant question is “Will these patients likely fail regionally, distantly, or both?”

Node Positivity In RCC: “Seek and Ye Shall Find”

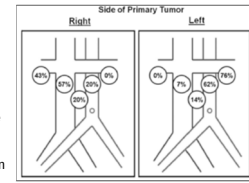


*608 patients
N+ rate = 13.6%
N+ rate was 3.4% vs. 10.5% when < 13 nodes compared to ≥ 13 nodes (Localized)
N+ rate was 19.7% vs. 32.2% when < 13 nodes compared to ≥ 13 nodes (Locally Advanced)

Tennore et al., BJU Int, 2003

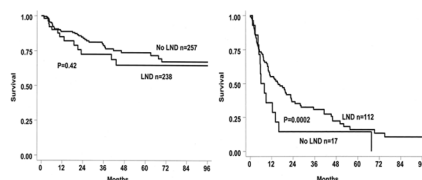


- When performing LND,
 - the paracaval and inter-aortocaval lymph nodes be removed in patients with **right-sided tumors**
 - the para-aortic and interaortocaval lymph nodes be removed in patients with **left-sided tumors**
 - from the crus of the diaphragm to the common iliac artery.



Location of +LN based on side of primary tumor. Percentage represents frequency of involved location in patients with lymph node-positive disease.

Importance Of Lymph Node Dissection In Surgery For Renal Cell Carcinoma



No Clinical Evidence Of Nodal Metastases

Pantuck et al. J Urol, 2003

Clinical Evidence Of Nodal Metastases

*No difference in RFS, M status not specified

RESULTS: n=68

RCC T_{any}, N_{any}, M_{any}
3201

RCC T_{any}, N_{any}, M0 RCC
2521

RCC T_{any}, N+, M0 RCC
68 (2.69%)

T_{any, p} N₊, M0 RCC

- Upfront Surgical Therapy:
 - 45% Disease Free at 12 months
 - 22% Long Term Disease Free Status
 - Median Follow Up 43.5 Months
- Papillary Histology
- pN1 v N2 (AJCC v6.0 2002)
- Sarcomatoid Features
- ECOG PS

Delacroix et al., J Urol, 2011

EORTC 30881: Lymph Node Dissection in Localized RCC

	Without lymph-node dissection (n=389)	With complete lymph-node dissection (n=383)	Hazard ratio	95% confidence interval	p value
Death	135 (35%)	137 (36%)	1.02	0.80-1.29	0.87
Local regional progression	34 (9%)	26 (7%)	0.77	0.46-1.28	0.31
Distant progression	58 (15%)	60 (16%)	1.05	0.73-1.50	0.81
Local or distant progression	93 (24%)	87 (23%)	0.95	0.71-1.27	0.70
Progression or death	156 (40%)	159 (42%)	1.02	0.82-1.28	0.84
Second primary	45 (12%)	36 (9%)	0.79	0.51-1.22	0.28

Blom et al., Eur Urol, 2008

EORTC 30881: Lymph Node Dissection in Localized RCC

		Without lymph-node dissection		With complete lymph-node dissection			p value
	pT category	n	%	n	%		
Death							0.87
Local regional progression	T0	5	1	4	1		0.31
Distant progression	T1	19	5	21	6		0.81
Local or distant progression	T2	230	65	221	63		0.70
Progression or death	T3	96	27	101	29		0.84
Second primary	T4	2	1	3	1		0.28
	TX	2	1	3	1		

Blom et al., Eur Urol, 2008

Intraoperative Nomogram For Triggering A Lymph Node Dissection: Mayo Clinic

Feature	Odds Ratio (95% CI)	p Value
Nuclear grade:		
1 + 2	1.0 (reference)	
3 + 4	5.25 (1.99-13.82)	<0.001
Sarcomatoid component	4.11 (2.08-8.12)	<0.001
Tumor 10 cm or greater	2.17 (1.27-3.70)	0.005
Primary tumor stage:		
pT1 + pT2	1.0 (reference)	
pT3 + pT4	2.00 (1.13-3.55)	0.017
Histological tumor necrosis	1.86 (1.00-3.48)	0.051

Blute ML et al., J Urol, 2004

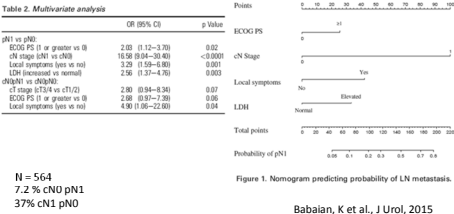
Intraoperative Nomogram For Triggering A Lymph Node Dissection: Mayo Clinic

Proportion of patients with regional lymph node involvement at nephrectomy by number of features in multivariate model

No. Features	No. pN0/pNx (%)	No. pN1/pN2 (%)
Total pts	1,584	68
0	726 (99.6)	3 (0.4)
1	299 (99.0)	3 (1.0)
2	264 (95.7)	12 (4.4)
3	183 (87.6)	26 (12.4)
4	105 (86.8)	16 (13.2)
5	7 (46.7)	8 (53.3)

Blute ML et al., J Urol, 2004

Clinical Predictors of Pathologically Positive Nodes



52 y/o with microscopic hematuria



Will this patient benefit from LND?

- Likely to be done laparoscopically
- Can an adequate LND be performed laparoscopically and what exactly is “adequate”?
- Arguably, in most cases, a LND will not be done

81 y/o undergoing evaluation for possible PE

- No PE found
- Incidental right renal mass
- No evidence of metastatic disease
- s/p open surgery for
 - Doweese clip for DVT
 - Cholecystectomy
 - Partial liver resection for abscess
 - Small bowel obstruction with resection

81 y/o undergoing evaluation for possible PE



81 y/o undergoing evaluation for possible PE

DIAGNOSIS

(A) RIGHT KIDNEY:
RENAL CELL CARCINOMA (4.0 CM IN GREATEST DIMENSION),
PAPILLARY TYPE 2, FUHRMAN NUCLEAR GRADE 3, INVASIVE INTO
RENAL PELVIS AND RENAL VEIN. (SEE COMMENT)
Margins of resection (ureteral, vascular and perinephric soft
tissue), no tumor present.

Two years later.....



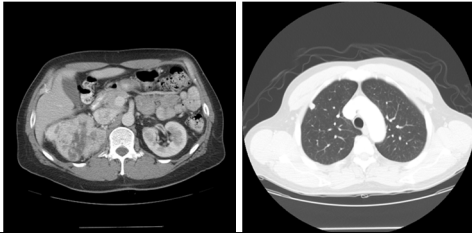
81 y/o undergoing evaluation for possible PE

(C) INTER AORTO/CAVAL, RETROCAVAL, PARACAVAL LYMPH NODES, STUMP OF RENAL ARTERY, STUMP OF RENAL VEIN, URETER:
METASTATIC RENAL CELL CARCINOMA, PAPILLARY TYPE, INVOLVING TWO OF TWENTY-EIGHT LYMPH NODES (2/28).
TUMOR MEASURES 3.0 CM IN GREATEST DIMENSION.
EXTRANODAL TUMOR EXTENSION PRESENT.
Vascular structures consistent with artery and vein and portion of ureter extensively denuded of urothelium with chronic inflammation and focal giant-cell reaction, no tumor present.

Is there a benefit to LND?

- This patient would have been saved from a second morbid surgery (older, more medical issues) if he underwent initial LND
- Unclear as to impact on outcome. Currently NED 1 year out

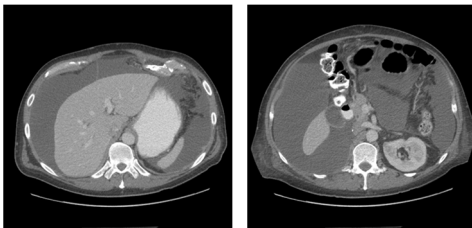
54 y/o presents with pulmonary nodules



54 y/o presents with pulmonary nodules

DIAGNOSIS
(A) RIGHT KIDNEY, ADRENAL, AND PARACAVAL LYMPH NODES :
RENAL CELL CARCINOMA (10 X 9 X 4.5 CM) CLEAR CELL TYPE,
FUHRMAN NUCLEAR GRADE 4.
WITH MULTIPLE SATELLITE NODULES (RANGING FROM 0.9-2.0 CM).
TUMOR INVADES PERINEPHRIC ADIPOSE TISSUE AND ADRENAL GLAND.
TUMOR PRESENT WITHIN MUSCLE CONTAINING VESSELS WITHIN THE RENAL SINUS.
Margins of resection (ureteral, vascular, and peripheral soft tissue), free of tumor.
No lymph nodes identified.
(B) PARACAVAL AND RETROCAVAL LYMPH NODES:
Five lymph nodes, no tumor present (0/5).

54 y/o presents with pulmonary nodules



54 y/o presents with pulmonary nodules

- Paracentesis with drain placement: Chylous ascites
- No fat diet versus TPN with drain
- Systemic therapy delayed indefinitely
- Did not benefit from, and possibly was harmed, by LND

The European Approach

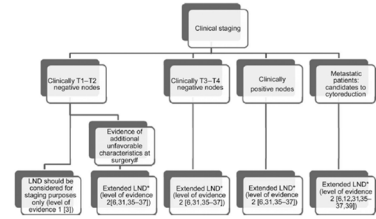
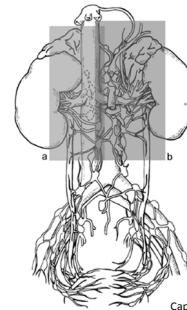


Fig. 1 - Rational algorithm for selection of renal cell carcinoma patient candidates for lymph node dissection (LND) at the time of radical nephrectomy. * = extra nodal/vascular invasion, ** = palpable nodes at surgery, larger tumors, conventional features, presence of negative tumor markers, and high histologic grade.

Capitanio, U et al. Eur Urol. 2011



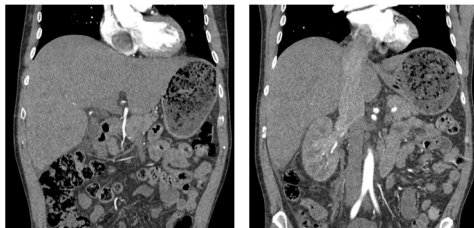
Capitanio, U et al. Eur Urol. 2011

The Role of Lymph Node Dissection in the Management of Renal Cell Carcinoma

- Role of lymph node dissection in locally advanced disease remains undefined
 - Evidence for improved cure rates with LND is lacking
- Improved staging in locally advanced disease is really the only argument to do it, but it implies something can be done to change outcome and that is not necessarily true to date
 - Would still advocate it for more locally advanced disease (where the money is!!!)
- Benefit of LND, with clinically negative nodes, in M1 disease, is completely uncharted waters that needs to be evaluated in the context of a clinical trial.
- Better designed phase III trial(s) are needed to define the role of LND in the appropriate population at risk for nodal disease

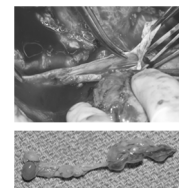
Surgical Strategy In Renal Cell Carcinoma With Venous Involvement

50 y/o WM presents with SOB and chest pain



Venous Tumor Thrombus (VTT)

- Most often ccRCC but occurs with all types
- Occurs with non-renal retroperitoneal tumors
 - Urothelial carcinoma
 - Adrenal tumors
 - Wilm's tumor
 - Metastases to kidneys
 - Others



VTT in RCC Patients

	Incidence %	Authors
•		
• Venous invasion	4-36	Skinner, 1972
•		Novick, 1980
•		Marshall, 1988
•		Hatcher, 1991
•		Poulliot, 2010
• IVC extension	3-5	Kearney, 1981
•		Libertino, 1987
• Atrial extension	0.5-1.0	Neves/ Zincke, 1987

VTT Presentation, n=303

Findings at presentation	Frequency
Microscopic hematuria	70%
Flank pain	46%
Fever	45%
Gross hematuria	42%
Anemia	23%
Incidental	19%
Mass	14%
LE edema	11%
Left varicocele	6%
Right varicocele	2%
Caput medusae	1%

Gettman et al, J Urol, 2003

Evaluation

- Thrombus identification
 - Contrast enhanced MRI remains gold standard as most accurate imaging modality
 - Sensitivity for thrombus is 100%
 - » Lawrentschuck, BJU Int 2005
 - » Kallman, J Comp Assist Tom, 1992
 - » Goldfarb, J Urol 1990
 - Multidetector CT
 - Sensitivity for thrombus is 84%
 - » Guzzo, J Urol 2009
- But MRI gives lots of additional information

MRI is superior for distinguishing tumor from clot

Level II Tumor Thrombus Partial Occlusion
Associated IVC Bland Thrombus



Evaluation

- Tumor thrombus can progress rapidly
 - Recent imaging is critical for surgical planning
- Staging as for any other advanced renal mass
- Consider anticoagulation
 - IVC occlusion or near occlusion
 - Presence of bland thrombus
- Please NO IVC filter preoperatively

Prediction of IVC Wall Invasion

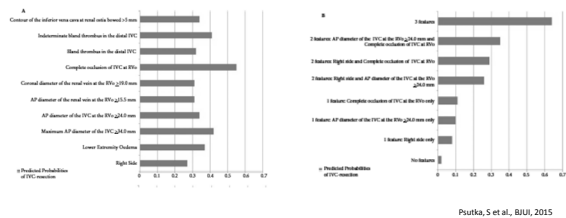
- Zini, J Urol 2008
- Determined that AP diameter of IVC and RV were associated with wall invasion
- IVC – 18 mm
- RV – 14 mm } 90% sensitivity

Mayo data, NCS 2010

RV > 21 mm, IVC > 32 mm assoc w/ wall invasion
For each 5 mm increase in diameter there is a 2-fold increased risk of wall invasion

If RV > 27 mm or IVC > 42 mm there was 100% invasion

Predictors of IVC Wall Resection During Thrombectomy



VTT Level Staging

Landmark	Staging systems				
	TNM	Neves	Novick	Hinman	Robson
Renal vein	T3a	0	I		
IVC <2cm above RV		I		I	IIa
IVC >2cm above RV	T3b	II	II		
IVC at hepatic veins		III	III	II	
Above diaphragm	T3c	IV	IV	III	

Adapted from Pouliot et al, J Urol 2010

Surgical Technique

- Pre-operative embolization for intracardiac or cavoatrial thrombi
 - Decrease intraoperative blood loss?
 - Vascularized thrombus regression
 - Rarely used anymore
- Midline or Chevron Incision
- Early arterial control key to reducing blood loss
- Ligasure useful for collateralizing vessels
 - Monitor for evidence of thrombus embolization
- Sternotomy for selected Level III and IV
 - Often can do transdiaphragmatic from the abdomen

Surgical Principles for Tumor Thrombectomy

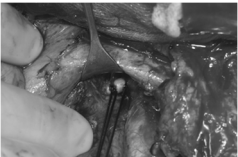
1. Assemble experienced team
 - Anesthesia
 - +/- Hepatobiliary, vascular, cardiac surgery
2. Operate on vessels first (preserve collateralized veins if IVC occluded)
3. Ligature renal artery, no need to embolize
4. Isolate venous structures
5. Completely remove thrombus
6. Manage any distal bland thrombus
7. Repair/patch/replace IVC as needed
8. Complete nephrectomy and LND

Preoperative Classification	n=160	Tumor Thrombus Presentation	Post Thrombectomy IVC Management
Group A IVC - No venous occlusion / No associated distal or bland thrombus	120 (75%)		
Group B IVC partially occluded / Distal pelvic bland thrombus	4 (2.5%)		
Group C IVC total / partial occlusion Associated bland thrombus	23 (14.4%)		
Group D IVC total occlusion Associated bland thrombus	13 (8.1%)		

Blute et al, J Urol 200

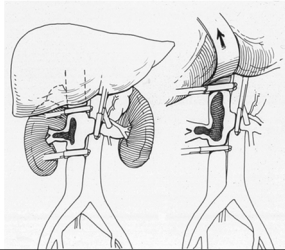
Avoid Preoperative Embolization

- Subramanian, Urology 2009
- IVC VTT cases 135 with, 90 without embolization
- Embolization associated with increased blood loss, increased complications, increased mortality
- MVA revealed 5 fold increased risk of perioperative death in patients with embolization



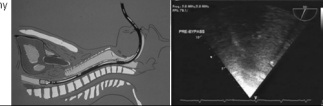
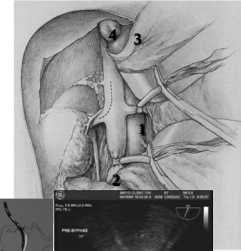
Tumor Thrombus: Level I or II Technique

- Occlude renal artery first
- Ligate hepatic veins from caudate lobe of liver
- Simple occluding maneuvers (contralateral vein, IVC inferior and superior to thrombus)

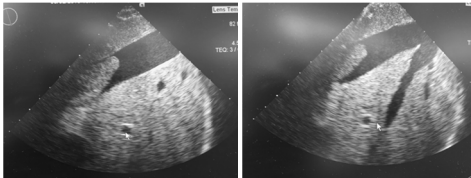


Tumor Thrombus: Level III Technique

- Renal artery ligation
- Mobilize liver for suprahepatic IVC access
- Sequence for venous control:
 - 1. Left renal vein
 - 2. Distal IVC, incl. 2nd lumbar vein
 - 3. Hepatic inflow (Pringle maneuver)
 - 4. Suprahepatic IVC (above thrombus)
- Remove thrombus
- Occlude IVC below hepatic inflow
- Release suprahepatic IVC & Pringle
- Repair vena cava leisurely
- Complete nephrectomy



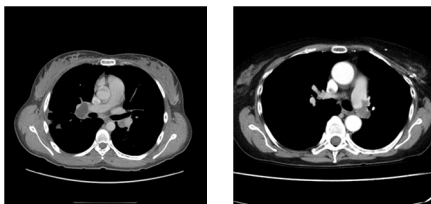
Intraoperative Ultrasound or TEE



Tumor Thrombus: Level IV Technique

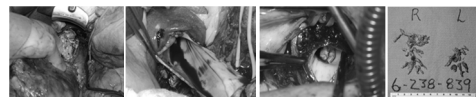
- Veno-veno bypass
- Cardiopulmonary bypass
- Cardiopulmonary bypass with hypothermic (16°C) circulatory arrest
 - Advantages: bloodless field, ~60 minutes of ischemia time
- Shuch et al, BJUI 2011
- Hypothermic arrest is associated with longer OS and significant reduction in perioperative mortality

Presence of Pulmonary Emboli

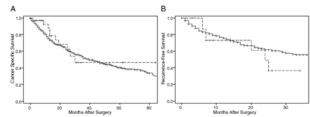


Tumor Thrombus Embolism

- Kayalar et al, J Thoracic CV surg, 2010
- Reviewed 9 cases of simultaneous RN, RPLND, IVC thrombectomy, and pulmonary embolectomy (7 bilateral, 2 unilateral)
- CP bypass in all 9, hypothermic arrest in 4
- 4 patients received adjuvant therapy
 - 2 patients alive at 4 and 56 months
 - 1 patient died of CVA at 62 months
 - 6 patients died of RCC at 6, 9, 12, 17, 25, & 29 months



Impact of Pulmonary Embolus at Presentation on Survival in IVC Thrombus Patients



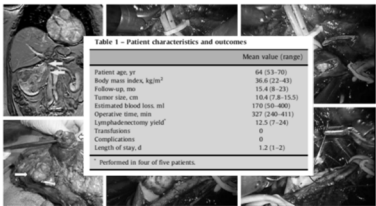
Abel EJ., et al, J Urol, 2013

Can minimally invasive approaches, including robotic assisted surgery be safely and effectively applied to the management of locally advanced RCC?



Initial Series of Robotic Radical Nephrectomy with Vena Caval Tumor Thrombectomy

Ronney Abaza *

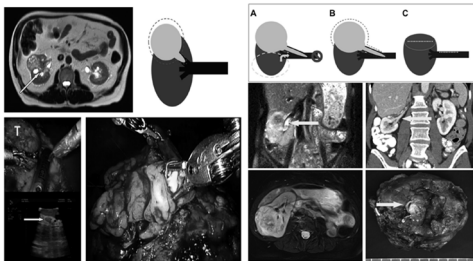


Eur Urol, 2011

Robotic Partial Nephrectomy for Renal Cell Carcinomas With Venous Tumor Thrombus

Ronney Abaza and Jordan Angel

N=4, 2/4 developed mets in < 1yr
Urology, 2013



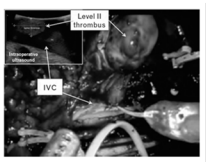
Robotic inferior vena cava thrombus surgery: novel strategies

Yi Sun^{a,b}, Andre Luis de Castro Abreu^a, and Inderbir S. Gill^a

"A total of 78 minimally invasive IVC thrombus cases have been reported in the literature" 67% Level 1, 30% Level 2, and 3% Level 3. Only 9 robotic cases have been reported.

KEY POINTS

- Level I renal vein thrombus: stapling the renal vein flush with the IVC achieves complete excision after careful intraoperative imaging with laparoscopic ultrasonography.
- Level II caval thrombus: for substantial level II involvement, complete caval isolation, including robotic control of infra-renal and supra-renal IVC, contra-lateral renal vein and lumbar veins is recommended.
- Level III caval thrombus: additional robotic maneuvers include control of short hepatic vein(s) for possible retro-hepatic IVC control, control of porta hepatis and even trans-thoracic thoracoscopic control of supra-hepatic IVC.



Curr Opinion Urol, 2014

RCC WITH VENOUS EXTENSION: MDACC 1993-2009

- 605 patients pT3
 - Median age 60.5 (28-90)
 - Follow-up 24.1 months
 - Median tumor size 10cm, 90% clear cell histology
 - 45% of patients N0M0
- Level of thrombus
 - 351 patients - renal vein or smaller branch veins
 - 208 patients - IVC below diaphragm
 - 42 patients - IVC above diaphragm

Abel et al., AUA 2011

SURGERY FOR RCC WITH VENOUS EXTENSION:MDACC 1993-2009

- Median EBL 900ml and operative time 186 min
- Hospital stay median 6 days
- Complications:
 - 25.4% first 30 days
 - 9.8% >30 days within 1st year
 - 58% transfusion rate
 - 2.6% 30 day mortality
- Overall survival
 - 66 months for N0M0 patients
 - 15 months for patients with nodal/ distant metastases

CLINICAL CHARACTERISTICS

Characteristic	No (%)
Thrombus level	
I	91 (34.3)
II	114 (43)
III	19 (6.8)
IV	41 (15.8)
M stage	120 (45.3)
N stage	46 (17.4)
N + M	31 (11.7)
Embolization	50 (18.9)

ALL COMPLICATIONS

Variable	Odds ratio(p-value)	
	UNIVARIATE	MULTIVARIATE
T3c	3.08 (0.01)	2.14 (0.329)
N+	0.89 (0.726)	-
HTN	1.38 (0.21)	-
DM	0.74 (0.344)	-
CAD	1.26 (0.598)	-
M+	0.85 (0.544)	-
M+N+	0.82 (0.62)	-
Pringle	3.23 (<0.001)	1.62 (0.336)
CP Bypass	6.22 (0.015)	3.63 (0.283)
Age≥60	2.53 (0.007)	2.26 (0.025)
Embolization	2.86 (0.008)	2.98 (0.018)

MAJOR COMPLICATIONS

Variable	Odds ratio(p-value)	
	UNIVARIATE	MULTIVARIATE
T3c	6.43 (<0.001)	4.23 (0.078)
N+	0.97 (0.929)	-
HTN	1.05 (0.873)	-
DM	0.44 (0.059)	-
CAD	1.34 (0.55)	-
M+	0.89 (0.7)	-
M+N+	0.87 (0.766)	-
Pringle	5.84 (<0.001)	2.78 (0.098)
CP Bypass	10.71 (0.002)	5.26 (0.198)
Age≥60	3.52 (0.004)	3.43 (0.022)
Embolization	2.97 (0.013)	4.4 (0.011)

MINOR COMPLICATIONS

Variable	Odds ratio(p-value)	
	UNIVARIATE	MULTIVARIATE
T3c	1.1 (0.851)	-
N+	0.94 (0.871)	-
HTN	1.13 (0.66)	-
DM	0.54 (0.086)	-
CAD	0.71 (0.496)	-
M+	0.75 (0.315)	-
M+N+	0.83 (0.675)	-
Pringle	2.28 (0.017)	1.22 (0.714)
CP Bypass	3.6 (0.111)	3.31 (0.325)
Age≥60	1.88 (0.091)	1.82 (0.124)
Embolization	2.78 (0.015)	3.01 (0.024)

MORTALITY

- Twelve patients (4.5%)
 - Intraoperative 1
 - Level IV thrombus
 - Metastases
 - Early (< 30 days) 10
 - Prolonged ICU stay, multiorgan failure
 - Late (30 days – 1 year) 1
 - Massive PE, at 3 months

PREDICTORS OF OVERALL SURVIVAL:

UNIVARIABLE AND MULTIVARIABLE ANALYSIS

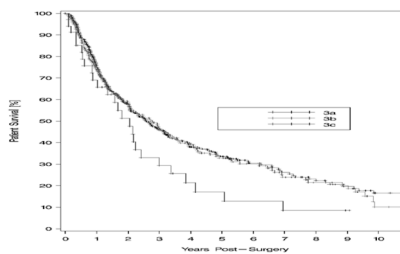
Variables evaluated:

- age
- gender
- side of tumor
- ECOG performance status
- pathologic features (tumor size, subtype, grade, sarcomatoid features, necrosis, peri-nephric fat invasion, hilar fat invasion, adrenal invasion, positive vein margins, positive surgical margins)
- lymph node metastasis
- distant metastasis
- symptoms at presentation
- time period when surgery was performed
- 2009 AJCC T stage.

Independent predictors of survival

- Clear cell subtype HR 0.55 (CI 0.4-0.8)
- Fuhrman grade IV 1.38 (CI 1.1-1.8)
- Sarcomatoid de-differentiation 1.58 (1.1-2.2)
- Peri-nephric fat invasion 1.50 (1.2-1.9)
- Lymph node metastasis 1.92 (1.5-2.5)
- Distant metastasis 2.30 (1.8-3.0)

Overall survival according to 2009 AJCC T stage



Tumor Thrombus and Survival

- Aggressive surgical resection with radical nephrectomy and IVC thrombectomy can potentially cure up to 70% of patients.

Table 1. Five-year survival for patients with RCC and IVC thrombus

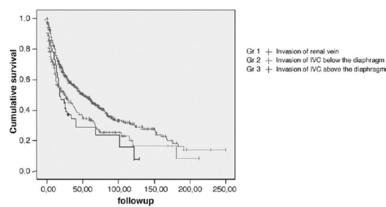
Authors (and date)	No. of patients	M0, %	M1, %
Novick et al ¹ (1992)	43	64	11
Swierczewski et al ² (1994)	100	64	20
Quek et al ³ (2001)	99	59	0
Zisman et al ⁴ (2003)	100	72	N/A
Blute et al ⁵ (2004)	191	59	15

RCC = renal cell carcinoma; IVC = inferior vena cava; M0 = no metastasis; M1 = distant metastasis; N/A = not available.

¹5-year survival

Otaibi, Tanguay 2007

Factors Predicting Outcome in T3b/c Renal Cell Carcinoma



Wagner et al., Eur Urol, 2009

Factors Predicting Outcome in T3b/c Renal Cell Carcinoma

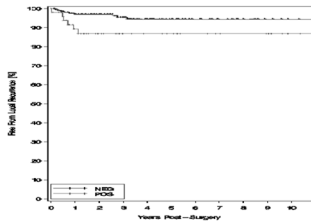
Prognostic factor	Multivariate analysis
IVC invasion	$p = 0.008$
Tumor size	$p = 0.013$
Fat invasion	$p = 0.003$
Lymph node metastasis	$p < 0.001$
Distant metastasis	$p < 0.001$
IVC, inferior vena cava.	

Wagner et al., Eur Urol, 2009

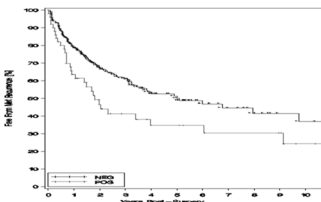
MICROSCOPIC POSITIVE VEIN MARGINS IN T3N0M0 PATIENTS ASSOCIATED WITH INCREASED LOCAL RECURRENCE AND METASTATIC PROGRESSION

- 270 T3N0M0 RCC patients undergoing surgery
- 19% of patients had cancer present at venous margin of resection
- Positive margins were more likely in patients with higher level thrombus ($p<0.001$) but no increased risk was detected based on Fuhrman grade ($p=0.28$).

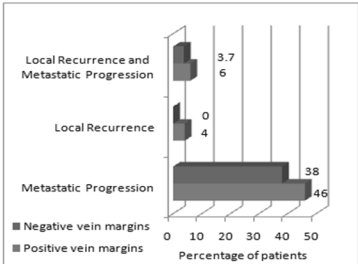
Positive vein margins in N0M0 patients associated with increased local recurrence



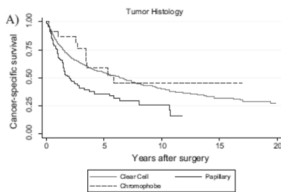
Positive vein margins in T3N0M0 RCC patients associated with increased metastatic progression



Presentation of Recurrent Disease

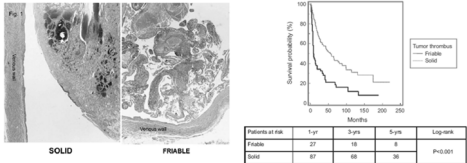


Outcomes Based On Histology In Patients With IVC Tumor Thrombi



Tilki, D et al., Eur Urol, 2013

Tumor Thrombus Consistency Predicts Cancer Specific Survival



Bertini R., et al., Eur Urol, 2011

Friable Thrombi Have Decreased Expression Of Cell Adhesion Molecules And Portend A Worse Prognosis

Table 4 Univariate and multivariate Cox analyses predicting overall survival in patients with RDx/MO disease (N = 119)

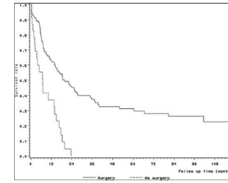
		Univariate analysis		Multivariate analysis	
		P	HR (95% CI)	P	HR (95% CI)
E-Cadherin	VTT				
	solid vs friable	0.009	2.027 (1.125-3.653)	0.009	3.227 (1.224-8.654)
	pT stage	0.163	1.464 (0.859-2.483)		
	pT8a vs pT7a	0.143	1.577 (0.867-2.962)		
	pT7a vs pT6a	0.738	1.487 (0.459-5.229)		
	pT6a vs pT5a	n.s.	n.s. (n.s.)		
Elastica-van-Gieson	Stromal grade	0.399	1.275 (0.753-2.129)		
	3 vs 1/2	0.606	1.211 (0.585-2.586)		
	3 vs 2	0.603	1.483 (0.591-3.848)		
	4 vs 2	0.742	0.221 (0.080-0.707)		
	VTT level	0.107	1.101 (0.616-1.962)		
	2 vs 1	0.322	1.420 (0.719-2.838)		
	3 vs 1	0.233	1.337 (0.639-2.833)		
	Histological subtype				
	Papillary vs clear cell	0.315	0.477 (0.113-2.013)		
	Squamous metaplasia				
	B1 vs B0	0.973	0.876 (0.235-3.483)		
	TN vs no TN	0.024	1.944 (1.091-3.472)	0.012	2.136 (1.185-3.850)
	Perinephric fat invasion				
	PF1 vs no PF1	0.083	1.723 (0.851-3.189)		

HR, hazard ratio; TN, tumour necrosis; PF1, perinephric fat invasion; n.s., not reached

Weiss et al., BJU, 2013

Non-operative Management of VTT

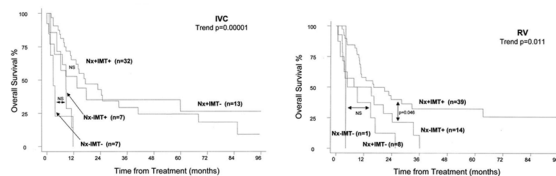
- Haferkamp, J Urol 2007
- 111 resected RCC with thrombus vs 23 conservative management



Median survival
Surgery – 19.8 mos
No surgery – 6.9 mos

Non-operative Management of VTT

- Zisman, J Urol 2003
- 207 patients with resected thrombus vs 44 non-operative



Targeted Therapy for Tumor Thrombus

- Multiple case reports of dramatic VTT reduction
 - Di Silverio, Urol Int 2008
 - Converted IVC thrombus to RV thrombus with 6 months sorafenib
- Shuch, BJU Int 2008
 - Conversion of level II to level I thrombus with 4 cycles of sunitinib
- Karakiewicz, Eur Urol 2008
 - Converted level IV to level I with 2 cycles sunitinib

EUROPEAN UROLOGY 55 (2011) 512–518
available at www.sciencedirect.com
journal homepage: www.elsevier.com/locate/eurol
Platinum Priority – Kidney Cancer
Editorial by Axel Hohenkottel on pp. 505–520 of this issue

The Impact of Targeted Molecular Therapies on the Level of Renal Cell Carcinoma Vena Caval Tumor Thrombus

Nicholas G. Costi^a, Scott E. Delacroix Jr.^a, Joshua P. Sleeper^a, Paul J. Smith^a, Rami F. Youssef^a, Brian F. Chaplin^a, Jose A. Karam^a, Stephen Culp^a, E. Jason Abel^a, James Bruggarolis^a, Ganesh V. Raj^a, Arthur I. Sagalowsky^a, Christopher G. Wood^a, Vitaly Margulis^{a,*}

- 25 pts with RCC + IVC VTT *in situ* received targeted Rx

- Therapy: sunitinib: 12 bevacizumab: 9
- temsirolimus: 3 sorafenib: 1

VTT level:	II	III	IV
	18	5	2

Targeted Therapy and in situ VTT

Cost et al, Eur Urol 2010

- Number of cases with change in tumor thrombus
- | | Level | Diameter |
|-------------|-------|----------|
| • Increased | 1 | 8 |
| • Stable | 21 | 2 |
| • Decreased | 3* | 11 |
- *1 each Level IV-III, level III-II, level II-I
- Regression limited to sunitinib treated patients

Impact of Pre-Surgical Targeted Therapy On Venous Tumor Thrombus

Table 2. Baseline Level of Venous Tumor Thrombus	
Level 0	60% (29/48)
Level 1	10% (5/48)
Level 2	21% (10/48)
Level 3	6% (3/48)
Level 4	2% (1/48)

Delacroix S et al., ASCO GU 2011

Table 3. Radiographic Characteristics of Patients with Clinically Meaningful Changes in Venous Tumor Thrombus										Clinically meaningful changes occurred in 25% of patients (12/48) table 3
Pt #	Initial Thrombus Level	Above Renal Vein (cm)	Below Renal Vein (cm)	Largest Diameter (cm)	→	Post Therapy Thrombus Level	Above Renal Vein (cm)	Below Renal Vein (cm)	Largest Diameter (cm)	
1	Level 3	4	0	3	→	Level 2	2	0	1.4	•Stable Disease in 75% 36/48
2	Level 2	2.5	0	1.6	→	Level 1	0.5	0	1.6	
3	Level 3	6.5	0	2.3	→	Level 2	5.1	0	1.7	•Progression occurred in 14.5% (7/48)
4*	Level 1	1.5	2.5	2.6	→	Level 1	0	0	1	
5*	Level 3	8.5	4	3.8	→	Level 3	8	0	3.9	•Regression in 10.4% (5/48).
6	Level 2	2.5	1	3.5	→	Level 3	3.5	1	2.75	
7	Level 1	0.5	1	1.76	→	Level 2	2.5	0	2.4	No Cases of Pulmonary Embolism
8	Level 0	0	0	2.1	→	Level 1	0.5	0	1.4	
9	Level 0	0	0	1.9	→	Level 1	0.5	0	1.6	
10	Level 0	0	0	1.6	→	Level 1	0.5	0	1.6	
11	Level 0	0	0	2.5	→	Level 2	5	4	2.8	
12*	Level 3	3.5	2.5	2	→	Level 3	4.5	2.5	2.1	

Progression

Regression

*: No Level Change but categorized as a change in surgical complexity
4*: Level 1 thrombus with regression to status of R/V (amenable to minimally invasive approach)
5*: Level 3 above hepatics to Level 3 at the level of the hepatics
12*: Level 3 thrombus at level of hepatics amenable to Pringle/intra-abdominal Surgery to Level 3 above hepatics (clinical increased complexity)

Delacroix S et al., ASCO GU 2011

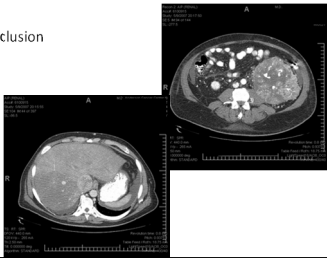
Systemic Therapy in VTT Cases

- If no evidence of metastases preferred option is surgical resection reserving systemic therapy for patients that are not surgical candidates
- In patients with metastatic disease performance status and relative burden of disease determine preop vs. post op vs. systemic therapy alone

BUDD-CHIARI SYNDROME

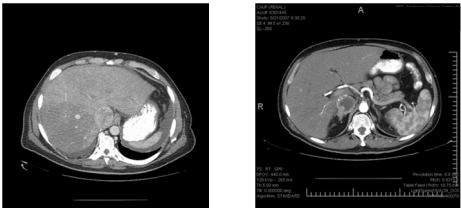
Hepatic Venous Outflow Occlusion

- Abdominal pain
- Ascites
- Hepatomegaly
- LE edema
- Abnormal LFT's



BUDD-CHIARI SYNDROME

MDACC APPROACH
Angioembolization → Interval resection



Summary

- Radical nephrectomy with IVC thrombectomy is a technically demanding surgery that can be associated with significant morbidity and mortality
- In the absence of metastases, nodal disease, sarcomatoid de-differentiation, and invasion into the perinephric fat or vein wall appear to predict prognosis
- Minimally invasive approaches are described but patient selection appears critical
- Pre-surgical treatment with either embolization or targeted agents does not appear to be helpful and in fact may worsen prognosis

T4 DISEASE

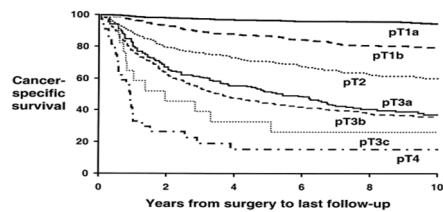


T4 Renal Cell Carcinoma

- Tumor invades beyond Gerota's fascia
 - Including contiguous extension into the ipsilateral adrenal gland
- Stage IV disease

AJCC Staging, 7th Edition, 2010

Outcomes for T4 disease



Frank I. J Urol 2005

Clinical T4 Disease

- 30 patients with cT4
- All underwent surgery
- Only 12 (40%) were pT4
- 18 (60%) were overstaged

Margulis V. Cancer. 2007

Baseline Characteristics

1992 to 2002
61 patients pT4

Variable	N (%)
Local symptoms	
Yes	36 (59)
No	25 (41)
Systemic symptoms	
Yes	42 (68.9)
No	19 (31.1)
Clinical (Preoperative) T stage	
<T4	19 (31.1)
T4	42 (68.9)
Clinical (Preoperative) N stage	
N0	29 (47.5)
N1	32 (52.5)
Clinical (Preoperative) M stage	
M0	22 (36.1)
M1	39 (63.9)

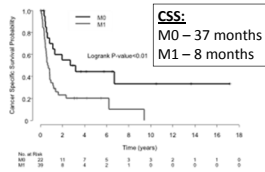
Borregales LD. Urol Onc. 2016

Pathology Characteristics

Variable	N (%)
Tumor diameter at nephrectomy, cm	13 (10 - 16)
Pathological N Stage	
N0	26 (42.6)
N1	16 (26.2)
Histology	
Clear Cell	47 (77.0)
Non-Clear Cell	14 (23.0)
Fuhrman grade	
3	14 (25)
4	39 (69.6)
Sarcomatoid dedifferentiation	
Yes	24 (39.3)
No	37 (60.7)

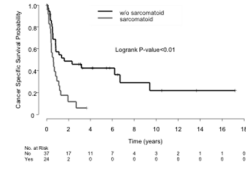
Borregales LD. Urol Onc. 2016

Cancer Specific Survival



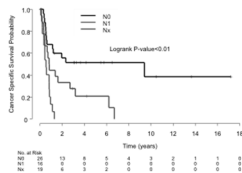
Borregales LD. Urol Onc. 2016

CSS (by sarcomatoid features)



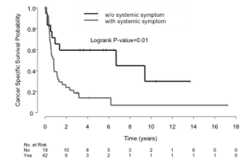
Borregales LD. Urol Onc. 2016

CSS (by Nodal stage)



Borregales LD. Urol Onc. 2016

CSS (by systemic symptoms)



Borregales LD. Urol Onc. 2016

Multivariate Analysis for CSS (using only Pre-operative Variables)

Variables	Multivariate	
	HR (95% CI)	P Value
Clinical N stage at diagnosis (N1 versus N0)	0.63 (0.33 – 1.22)	0.17
M stage at diagnosis (M1 versus M0)	1.77 (0.81 – 3.85)	0.15
Abnormal LDH (Yes versus No)	3.97 (1.87 – 8.43)	<0.01
Abnormal Alkaline Phosphatase (Yes versus No)	2.92 (1.47 – 5.80)	<0.01

Borregales LD. Urol Onc. 2016

Multivariate Analysis for CSS (using only Post-operative Variables)

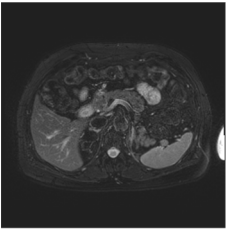
Variables	Multivariate	
	HR (95% CI)	P Value
Sarcomatoid dedifferentiation (Yes versus No)	3.11 (1.51 – 6.42)	<0.01
Pathological N Stage		
pN1 versus pN0	5.16 (1.94 – 13.69)	<0.01
pNx versus pN0	2.58 (1.15 – 5.79)	0.02
M stage (M1 versus M0)	2.24 (1.01 – 4.98)	0.05
Abnormal LDH (Yes versus No)	2.32 (1.04 – 5.17)	0.04
Abnormal Alkaline Phosphatase (Yes versus No)	4.29 (2.04 – 9.00)	<0.01

Borregales LD. Urol Onc. 2016

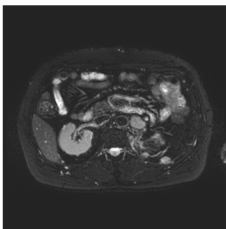
T4-Take Home Messages

- Survival in patients with pT4 RCC remains poor
 - Median survival of 10 months
- Preoperative identification of patients with pT4 disease is in need of refinement
 - May help improve patient counseling, management, and selection for inclusion in neoadjuvant/presurgical trials

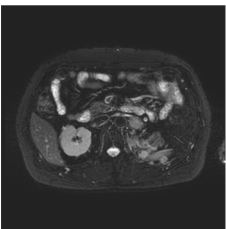
Local Recurrence after Radical Nephrectomy



Local Recurrence after Radical Nephrectomy



Local Recurrence after Radical Nephrectomy



Local Recurrence after Radical Nephrectomy

- Incidence of <5%

Local Recurrence: USC

- 11 patients
 - 10 with no metastases at presentation
- Most patients had symptoms
- Presented 31 months after initial surgery
- 2 postoperative deaths
- 2 died of cancer at 8 and 22 months
- 3 died of causes unrelated to cancer recurrence
- 4 patients were without disease at a follow-up of 35, 46, 48 and 211 months

Esrig D. J Urol. 1992

Local Recurrence: MDACC

- 16 patients with locally recurrent RCC
 - 8 patients received neoadjuvant Rx, 7 of these received additional adjuvant Rx
 - 7 IFN α based
 - 1 IL-2 based
 - Neoadjuvant group - 50% no evidence of cancer
 - Surgery alone group - 25% no evidence of cancer

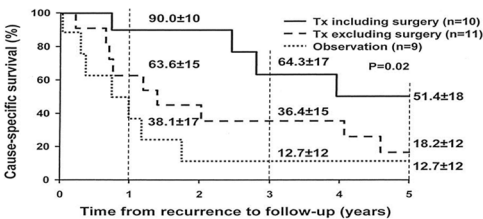
Tanguay S. J Urol. 1996

Local Recurrence: MDACC

- 15 patients had complete resection (of the 16)
 - 12 had clear margins → 6 were free of cancer
- 12 of the 16 were alive at 2 years after second surgery

Tanguay S. J Urol. 1996

Local Recurrence: Mayo Clinic



Itano NB. J Urol. 2000

Local Recurrence: MD Anderson Experience

- 1990-2014
- 102 patients had surgery for local recurrence
- 84.3% of the patients → radical nephrectomy at outside institutions → subsequently referred to MDACC for local recurrence surgery

Thomas AZ. J Urol. 2015

Local Recurrence: MD Anderson Experience

- Time from nephrectomy to local recurrence diagnosis was 1.5 years
- At time of nephrectomy
 - Median age 55 years
 - 79.4% had open surgery
 - 60.8% were pT3-4 (invading renal vein/vena cava, fat or other organs)
 - 19.6% were pN1 (positive lymph nodes)
 - 13.7% had positive margins

Thomas AZ. J Urol. 2015

Local Recurrence: MD Anderson Experience

- Area of local recurrence
 - 48% - Soft tissue/renal fossa
 - 40.2% - Lymph nodes
 - 11.8% - Adrenal gland
- At time of local recurrence surgery
 - 41.2% had symptoms
 - 45.1% received neoadjuvant Rx

Thomas AZ. J Urol. 2015

Local Recurrence: MD Anderson Experience

- Median local recurrence size = 4.5cm
- Open surgery for 97.1% of patients
- Major complications = 14.7%
- Blood loss = 700 mL
- Median surgery duration = 3.5 hours
- Median hospital stay = 1 week

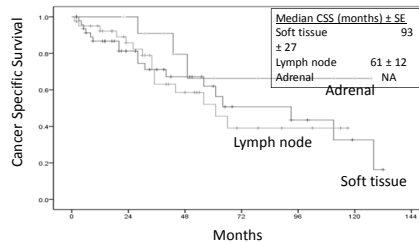
Thomas AZ. J Urol. 2015

Local Recurrence: MD Anderson Experience

- 58.8% of patients had cancer relapse after local recurrence surgery
 - Median time to second relapse ~ 2 years
 - Median survival after second relapse ~5.5 years
- Predictors of worse outcomes after surgery for local recurrence
 - Positive lymph nodes at time of initial nephrectomy
 - Larger size of local recurrence

Thomas AZ. J Urol. 2015

CSS-by Site of Recurrence



Thomas AZ. J Urol. 2015

Resection of Isolated Retroperitoneal LN Recurrence

- 50 patients, 4 tertiary centers
- Median (IQR) time to RPLN recurrence after nephrectomy → 12.6 (6.9-39.5) months
- Median (IQR) follow-up after RPLN resection → 28.0 (13.7-51.2) months
- 26 patients developed RCC recurrence, at a median (IQR) of 9.9 (4.0-18.5) months after RPLN resection

Russell CM. BJU Int. 2016

Resection of Isolated Retroperitoneal LN Recurrence

- 11 patients subsequently died (10 DOD)
- Median PFS after RPLN resection → 19.5 months
 - 5-year PFS → 35.4%
- RPLN recurrence at ≤12 months after nephrectomy → with a significantly ($p=0.003$) inferior median PFS (12.3 months) compared with RPLN recurrence at >12 months after nephrectomy (47.6 months)

Russell CM. BJU Int. 2016

Resection of Recurrent IVC Thrombus

- 16 patients (1970-2013)
 - 3 synchronous widely metastatic disease → no surgery (DOD <6 mo)
 - 13 → surgery
 - Median time from prior nephrectomy to diagnosis of 6 mo (range: 3-58)
 - Surgical resection was completed in 11 (2 unresectable)- median blood loss 2500 ml (range: 200-7000)
 - Median time to recurrence → 4mo
 - Median time to death → 12 mo
 - All patients recurred and died of disease (median follow-up of 12 mo)

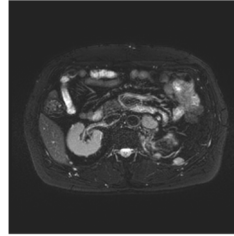
Parker WP. Eur Urol Focus. 2016

SABR of IVC Thrombus

- 2 cases of level IV thrombus treated with SABR (50Gy, 36Gy) → Alive at 2 years, and at 18 months
- Ongoing prospective trial
 - [NCT02473536](#)

Hannan R. Cancer Biol Ther. 2015

Local Recurrence after Radical Nephrectomy



Treatment

- Resection of all retroperitoneal masses
- Resection of renal artery and vein stump
- Distal pancreatectomy (Thanks M. Katz!)
- Splenectomy
- Left hemicolectomy
- Left adrenalectomy
- Omentectomy
- Partial diaphragm resection
- RPLND

→ NED 21 months postop

Take Home Messages

- Local recurrences are rare but can occur after initial treatment
- Important to follow-up with urologist after initial treatment
- Best treated in referral medical centers



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Kidney Cancer: Laparoscopic Management

Andrew A. Wagner, MD
Director of Minimally Invasive Urologic Surgery
Co-Director Kidney Tumor Clinic
Beth Israel Deaconess Medical Center
Associate Professor of Surgery
Harvard Medical School

Disclosure Statement

- Nothing to disclose



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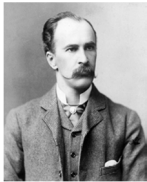


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"Diseases that harm require treatments that harm less" -Sir William Osler



Osler c. 1880

- One of four founding physicians of Johns Hopkins
- Created first residency program
- Developed first bedside teaching curriculum
- "Father of Modern Medicine"



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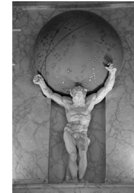
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Origin of the word Laparoscopy

Greek words *lapara*, meaning "the soft part of the body between ribs and hip, flank, loin" and *skopein*, meaning "to look at or survey."



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Outline

- History of laparoscopic management for kidney cancer
 - Radical nephrectomy
 - Partial nephrectomy
 - Robotic surgery
- AUA Guidelines
- Approaches and Techniques
 - Surgical Planning
 - Radical nephrectomy
 - Partial nephrectomy
 - Cytoreductive surgery/advanced RCC/IVC thrombectomy
- Disadvantages and pitfalls of laparoscopy



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History of Laparoscopic Surgery for Kidney Cancer

- 1990 First Laparoscopic Radical Nephrectomy: Clayman et al (NEJM May 1991)
 - Washington University, St Louis
 - 85 yo woman
 - 3 cm mass
 - IRB approval
 - 7 hours, each segmental artery individually clipped
 - Kidney morcellated in lap sac and removed through 11mm port
 - 1 u transfusion postop
 - Oncocytoma
- Clayman et al. letter response to NEJM editor Oct 1991:
 - "In the next few years minimally invasive surgery will probably come of age. Laparoscopic cholecystectomy, ovariectomy, hysterectomy, appendectomy, nephrectomy and even colectomy may well become standard procedures"
- By 1995: 160 publications on "laparoscopic nephrectomy"



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First Laparoscopic Nephrectomy on June 25, 1990, with Ralph Clayman (left), Louis Kavoussi (behind Clayman on right) and Steve Dierks (far right)



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History of Laparoscopic Surgery for Kidney Cancer

- Reports of retroperitoneal approach, nephroureterectomy, lap partial nephrectomy, and retroperitoneal PN soon followed
- Hand assisted surgery afforded surgeons without extensive laparoscopic training the ability to perform LN while maintaining the benefits of minimally invasive surgery
- Retroperitoneal surgery remained challenging due to lack of dilating balloons, small working space, difficulty maintaining pneumoperitoneum
- Concerns remained about morcellation and tumor spillage, cancer control, difficult learning curve, few laparoscopically trained urologists.
- However early studies demonstrated early recovery and less pain medicine requirements for LRN
 - McDougall et al J Urol 1996: compared 17 LRN to 12 ORN
 - Decreased morphine requirements, time to normal activity, time to full recovery

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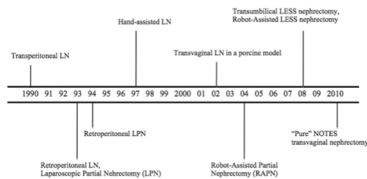


Figure 2. Timeline of new techniques in laparoscopic nephrectomy

From Kerbl et al. J Urol March 2011

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LAPAROSCOPIC RADICAL NEPHRECTOMY FOR RENAL TUMOR: THE WASHINGTON UNIVERSITY EXPERIENCE

ELSPETH M. McDOUGALL,* RALPH V. CLAYMAN AND OSAMA M. ELASHRY

From the Division of Urologic Surgery and Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri

- McDougall et al J Urol 1996: compared 17 LRN to 12 ORN
 - Op time LRN 6.6 vs ORN 2.3 hrs
 - Hospital stay LRN 4 vs ORN 8 days
 - Decreased morphine requirements, time to normal activity, time to full recovery after LRN
- Lessons learned:
 - Obtaining pneumoperitoneum in lateral position saves time
 - No need for preoperative stent placement
 - Prefer to remove intact specimen
 - High rate of incisional hernias with flank extraction incision compared to lower midline incision
 - Total charges for LRN \$2000 higher than ORN

J Urol 1996, 155:1180

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History of Laparoscopic Surgery for Kidney Cancer

- Reports of equivalent cancer control led to increased adoption of LRN
 - Chan et al J Urol 2001: no difference in disease free survival between LRN and ORN
 - By 2000 55% of cases at Johns Hopkins were performed as LRN (Permpongkosol et al BJU Int 2006)

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History of Laparoscopic Surgery for Kidney Cancer

- Robotic Radical Nephrectomy?
 - Although Lap RN is completely extirpative and does not require suturing, Robotic RN has gained in popularity despite its increased costs
 - Jeong et al. JAMA 2017



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JAMA | Original Investigation

Association of Robotic-Assisted vs Laparoscopic Radical Nephrectomy With Perioperative Outcomes and Health Care Costs, 2003 to 2015

In Gab, Jeong, MD, PhD; Yesh S. Khundwala, BS; Jee Heon Kim, MD, PhD; Deok-Hyun Han, MD, PhD; Shuefang Li, MS; Ye-Wang, PhD; Steven L. Chang, MD; Benjamin I. Chung, MD



- Premier database evaluation of >23000 patients after Lap and Robotic RN
 - Laparoscopic RN 18500 vs Robotic RN 5000
- Use of Robotics for RN: 1.5% in 2003 to 27% in 2015
- No difference in major complications
- Prolonged operating time for Robotic RN (46% vs 26% > 4 hours)
- Increased overall hospital costs with Robotic RN
 - \$19530 vs \$16851

JAMA 2017;318:1561

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History of Laparoscopic Partial Nephrectomy

- 1995 first publication by Winfield et al. J Urol
 - University of Iowa, Iowa City, IA
 - 6 patients, all with presumed benign problems
 - Op time 6 hours
 - All had ureteral catheters placed
 - Argon used to coagulate
 - No hilar control/clamping
 - No suturing of collecting system performed
 - 2 patients underwent open conversion

LAPAROSCOPIC PARTIAL NEPHRECTOMY: INITIAL EXPERIENCE AND COMPARISON TO THE OPEN SURGICAL APPROACH

HOWARD S. WINFIELD, JAMES F. DONOVAN, GREG O. LUND, KARL J. KREIDER, KENNETH E. STANLEY, BRUCE P. BROWN, STEFAN A. LOENING and RALPH V. CLAYMAN*

From the Department of Urology, University of Iowa College of Medicine, Iowa City, Iowa



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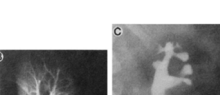


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History of Laparoscopic Partial Nephrectomy



LAPAROSCOPIC PARTIAL NEPHRECTOMY: INITIAL EXPERIENCE AND COMPARISON TO THE OPEN SURGICAL APPROACH

DIWAKAR S. SINGH, JAMES F. BOWMAN, GREG G. LIND, KYLE J. BISHOP, KENNETH S. STANLEY, BRUCE F. BROWN, STEVEN A. LUNDQUIST, and RAUL V. CLAYTON*

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J Urol 153,1409, 1995



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History of Laparoscopic Partial Nephrectomy: Concerns

Comparison of 1,800 Laparoscopic and Open Partial Nephrectomies for Single Renal Tumors

*Indefrick R, Gill, Leslie R, Kaveion, Brian R, Lane, Michael L, Hsiao, Deanne Robinson, J. Roberto Colombo, Jr, Igor Fajana, Christopher M. Weigelt, Andrew H. Koenig, Michael W. Kattan and Christopher C. Norlick**

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- Indications expanded to include solid masses
- Concerns remained about difficult learning curve, complications despite presumed earlier recovery
- Gill et al J Urol 2007: Hopkins, Mayo, Clev Clinic 1800 patients
 - Despite open partial patients being more complicated, Lap partial patients had longer ischemia time, more complications, more secondary procedures
 - Renal functional outcomes similar at 3 months

J Urol 2007; 178: 41-6

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History of Laparoscopic Partial Nephrectomy

- Indications expanded further and soon included hilar tumors, larger T1b tumors, central tumors, solitary kidneys, heminephrectomy, obese patients, patients after prior surgery
- In fact very few patients were not eligible for laparoscopic approach
- Soon comfort level permitted earlier unclamping which reduced the WIT by 50%

From Gill et al. J Urol 183: 2010

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History of Laparoscopic Partial Nephrectomy

- 7 year oncologic outcomes published by Lane and Gill, Cleveland Clinic
- No difference in outcomes with up to 7 years of follow-up
- 1600 patients with minimum 1 year f/u

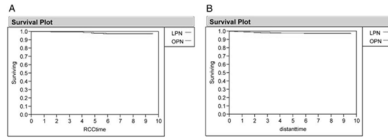


Figure 1. Kaplan-Meier estimates of cancer specific (A) and metastasis-free (B) survival after LPN and OPN.

J Urol Vol. 183, 473-479, February 2010

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Robotic Partial Nephrectomy: First Report

ROBOTIC-ASSISTED LAPAROSCOPIC PARTIAL NEPHRECTOMY: TECHNIQUE AND INITIAL CLINICAL EXPERIENCE WITH daVINCI ROBOTIC SYSTEM
MATTHEW T. GETTMAN, MICHAEL L. BLUTE, GEORGE K. CHOW, RICHARD NEURURER, GEORGE HARTSCH, AND BENJAMIN FROELICH

- 2002-2003, 13 patients at Mayo Clinic, Rochester, MN
- 8 cases used intra-arterial cooling prior to clamping
- 2 cases retroperitoneal, 11 trans peritoneal
- Median diameter 3.5 cm
- EBL 170cc
- WIT 22 min; CIT 33 min.
- One positive margin without residual tumor on radical nephrectomy

Gettman et al. Urology. 64: 914. 2004

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Robotic Partial Nephrectomy Versus Laparoscopic Partial Nephrectomy for Renal Cell Carcinoma: Single-Surgeon Analysis of >100 Consecutive Procedures

Agnes J. Wang and Sam B. Bhayani

- 2009 Wash U experience
- 100 consecutive patients
- Shorter WIT in Robotic group
- Shorter op time than prior series
- Use of the 'sliding clip renorrhaphy'

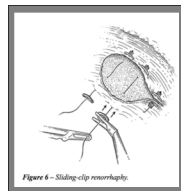


Figure 6 - Sliding clip renorrhaphy

Urology 73:306. 2009

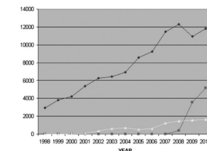
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Robotic Partial Nephrectomy: Rapid Dissemination

- Ghani et al J Urol 2014, NIS from 2008-2010
 - In 2010 annual increase in open, robotic and lap RN was:
 - OPN 7.9%
 - Robotic PN 45%
 - LPN 6.1%
 - Postop complication RPN vs OPN
 - OR 0.63 (0.55-0.72). P <0.001



J Urol 2014;191: 907-13

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Complications After Robotic Partial Nephrectomy

Table 1 Summary of RAPN perioperative complications by study

Study	Number of patients	Years enrolled	Intraop. complication rate	Conversion to PN (non-RAPN)	Conversion to RN	Postop. complication rate	Clavien 1-2	Clavien 3-4	Clavien 5
Tanagho et al., 2013 [9-1]	886	2007-2011	2.6 %	0.3 %	0.5 %	12.1 %	3.6 %	0 %	0 %
Mathies et al., 2013 [10]	240	2009-2011	n/a	n/a	n/a	22.5 %	10.4 %	0 %	0 %
Figueroa et al., 2012 [11]	347	2008-2010	2.9 %	0 %	0.6 %	8.9 %	2.9 %	0 %	0 %
Spina et al., 2011 [12]	450	2006-2009	1.8 %	0.7 %	1.6 %	12.0 %	3.8 %	0 %	0 %
Kawak et al., 2011 [13]	252	2007-2010	2.0 %	2.0 %	0 %	16.7 %	2.4 %	0 %	0 %
Hamway et al., 2010 [14]	183	2006-2008	2.7 %	1.1 %	0 %	3.8 %	3.3 %	0 %	0 %
Scoll et al., 2010 [15]	100	2007-2009	n/a	1.0 %	1.0 %	7.0 %	5.0 %	1.0 %	1.0 %
Rogers et al., 2008 [16]	148	2002-2007	n/a	1.4 %	0 %	6.8 %	2.0 %	0 %	0 %

Intraop. = intraoperative; PN = partial nephrectomy; RN = radical nephrectomy; postop. = postoperative

From Kim et al Curr Urol Rep 2014

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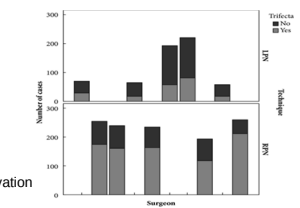
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Comparing Robotic PN to Laparoscopic PN

- Trifecta:
- WIT <25 min
 - Neg margins
 - No complications

- Optimal outcome (pentafecta):
- No CKD upstaging
 - Minimum 90% total eGFR preservation



From Zaiger et al. BJU 2015

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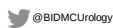
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Comparing Robotic PN to Laparoscopic PN

- Choi et al Eur Urol 2015
- Meta analysis LPN vs RPN
- 23 studies, 2240 patients
- RPN:
 - Lower conversions to radical and open surgery
 - Shorter WIT
 - Less change in eGFR
 - Shorter LOS



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AUA Guideline

Renal Mass and Localized Renal Cancer: Published 2017

- Ultimately, the decision for management strategy—RN, PN, or Ablation—should be made irrespective of approach available and physicians should employ minimally invasive approaches only when oncological, functional, and perioperative outcomes are unlikely to be compromised
- **Guideline Statement 22**
 - In patients undergoing surgical excision of a renal mas, a minimally invasive approach should be considered when it would not compromise oncologic, functional and perioperative outcomes. (**Expert Opinion**)



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Laparoscopic Management of Kidney Cancer: Approaches and Techniques

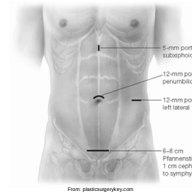
- Radical Nephrectomy
 - Standard LRN, NOTES, LESS, IVC thrombectomy
- Partial Nephrectomy
 - Robotic
 - Transperitoneal vs Retroperitoneal
 - Risk factors for CKD after PN
 - Resection techniques
 - Standard vs enucleation
 - Clamping Techniques
 - Standard vs early vs selective vs non clamped
 - Renorrhaphy Techniques
 - Standard with bolster vs no bolster



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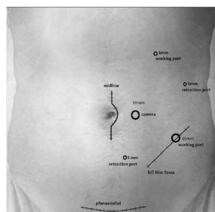
Laparoscopic Management of Kidney Cancer: Radical Nephrectomy Incisions



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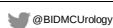
Laparoscopic Management of Kidney Cancer: Various extraction incisions and hand port incisions



From Adlyat et al. Int J Urol 2013

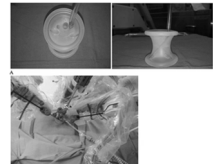


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LESS and NOTES in Laparoscopic Kidney Surgery

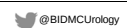
- LESS: Laparoendoscopic Single Site Surgery
 - Usually requires Single Incision port, laparoscopic or robotic approaches possible
- Majority of cases are radical nephrectomy
- Fan et al. meta-analysis, Eur Urol 2012
 - Longer operative time, Higher conversion rate
 - Possibly lower pain/analgesics/hosp stay
 - No difference in complications
- Shin et al BJUI 2014
 - LESS PN vs Standard PN (n =167)
 - Longer WIT with LESS, 26 vs 20 min
 - Lower VAPS at discharge (2.1 vs 1.7)
 - Is this clinically meaningful?



From Kim et al. Int J Surg. 2016



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LESS and NOTES in Laparoscopic Kidney Surgery

- NOTES: Natural Orifice Transluminal Endoscopic Surgery
- Possible sites of entry: stomach, colon, vagina, bladder

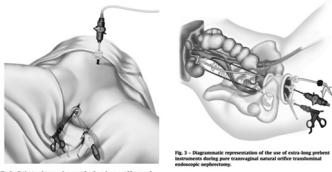
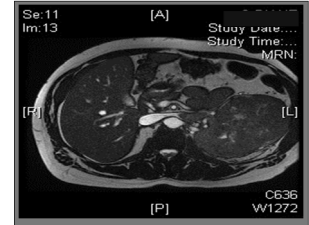


Fig. 1 - Patient and incision placement for the subsequent 25 cases of transvaginal natural orifice transabdominal endoscopic nephrectomy.

Fig. 2 - Diagrammatic representation of the use of extra long probes transvaginal entry and transcolonic natural orifice transabdominal endoscopic nephrectomy.

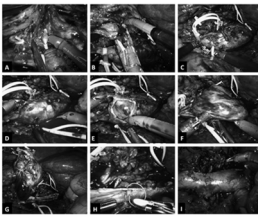
From Xue et al Eur Urol 2015

Laparoscopic Radical Nephrectomy: Renal Vein and IVC Thrombectomy



Laparoscopic Radical Nephrectomy: Renal Vein and IVC Thrombectomy

- Laparoscopic/Robotic IVC thrombectomy



From Chopra et al Eur Urol 2017

- First reported in 2011
- 2016: Abazza et al. reported on 32 cases by 9 surgeons
- IVC was cross clamped in 24 cases
- No conversions to open surgery
- Avg op time 292 min, 3 transfusions
- No Clavien III-V complications

Laparoscopic and Robotic Partial Nephrectomy

- Surgical Planning
- Approaches/port placements
- Clamping
- Resection
- Renorrhaphy

Surgical Planning

- Size
- Hilar anatomy
- Involvement of renal vein
- Proximity to sinus/collecting system
- Inflammation near surrounding structures?
- Amount of peri-renal fat
- Vasculature
 - Arteries, veins, location, number, proximity
 - Lumbar veins, accessories, gonadals
- Opposite kidney, any issues?

Surgical Planning: Abnormal Left Hilum



Surgical Planning: Contralateral Kidney



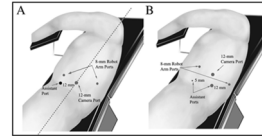
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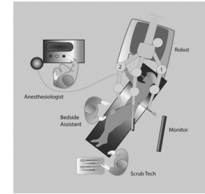
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Surgical Planning : Transperitoneal vs Retroperitoneal?

- Anterior/posterior?
- Upper pole?
- Amount of retroperitoneal fat?



From Hu et al Eur Urol 2014

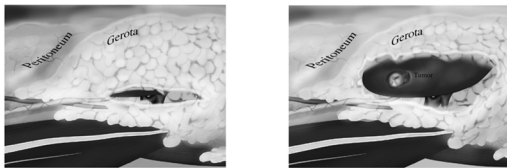


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Surgical Planning : Transperitoneal vs Retroperitoneal?



From Hu et al Eur Urol 2014

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Surgical Planning : Transperitoneal vs Retroperitoneal?

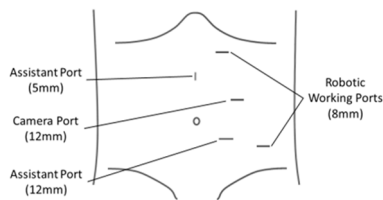
- Retroperitoneal PROS
 - lateral or posterior tumors
 - Avoids bowel mobilization
 - Direct access to renal hilum
 - Shorter overall OR time and hospitalization (Pavan et al J Endourol 2018)
- Retroperitoneal CONS
 - Smaller working space
 - Unfamiliar anatomy/absent landmarks
 - Difficulty accessing lower pole tumors and anterior tumors
 - More difficult in obese patients
- Therefore RP approach may be particularly advantageous for posterior upper pole and perihilar tumors, and it might translate into shorter OT and hospital stay

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Transperitoneal Robotic Partial Nephrectomy Ports: LEFT

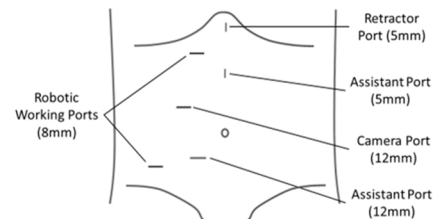


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Transperitoneal Robotic Partial Nephrectomy Ports: RIGHT



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Standard vs Early Unclamping Technique



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Standard vs Early Unclamping Technique (EU)

- EU May be more applicable (than selective clamping) to majority of robotic surgeons as it does not require dissection of tertiary vessels
- WIT is typically <15 min.
- Risk of delayed complications including urine leak and pseudoaneurysm extremely low
 - Of 403 patients after RPN at BIDMC using early unclamping without bolsters or fibrin glue products: one urine leak (in pt with complex pyelolithotomy on IS) and no episodes of delayed bleeding or pseudoaneurysm
 - Likely due to suturing of collecting system and sinuses under direct vision. Also direct suturing of arterial bleeders after unclamping.

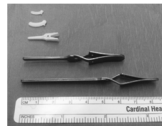
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Laparoscopic/Robotic Partial Nephrectomy Techniques: Super Selective Clamping

- Lap/robotic dissection of tertiary renal vessels supplying tumor
- Control of vessels followed by tumor resection
- disposable neurovascular aneurysm microsurgical bulldog clamps used



EUROPEAN UROLOGY 61 (2012) 67–74



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Anatomic Renal Artery Branch Microdissection to Facilitate Zero-Ischemia Partial Nephrectomy

Casey K. Ng, Inderbir S. Gill¹, Mukul B. Patel, Andrew J. Hung, Andre K. Berger, Andre Luis de Castro Abreu, Masahiko Nakamoto, Manuel S. Eisenberg, Osamu Ukimura, Duraiyah Thangathurai, Monish Aron, Mihir M. Desai

- 22 pts after zero ischemia; 22 pts after standard
- No difference in op time (both > 4hrs)
- No difference in EBL, complications
- No difference in 2 month creatinine



EUROPEAN UROLOGY 61 (2012) 67–74

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Robotic Partial Nephrectomy with Superselective Versus Main Artery Clamping: A Retrospective Comparison

Mihir M. Desai¹, Andre Luis de Castro Abreu, Scott Leslie, Jai Cai, Eric Yi-Hsiu Huang, Pierre-Marie Lewandowski, Dennis Lee, Arjun Dharma Raja, Andre K. Berger, Alvin Goh, Osamu Ukimura, Monish Aron, Inderbir S. Gill

- Robotic superselective clamping
- 58 superselective PN; 63 standard RPN
- Op time 301 min for superselective; 229 standard
- Superselective tumors larger and more hilar location
- Bolsters used in 41% and 32%
- Transfusion: 24% and 6%
- Superselective : 3 urine leaks, PE
- Standard : 1 urine leak, PE
- Change in eGFR was -11% and -17% with f/u 4-6 months (p=0.03)

EUROPEAN UROLOGY 66 (2014) 712–719

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Laparoscopic/Robotic Partial Nephrectomy Techniques: Zero Ischemia – “OFF Clamp” Partial

- Lap or Robotic resection without any hilar clamping
- Very challenging procedure due to ongoing blood loss and poor visualization
- No ischemia to segmental or entire kidney, thus is there a renal functional benefit?

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To clamp or not to clamp? Long-term functional outcomes for elective off-clamp laparoscopic partial nephrectomy

Paras H. Shah*, Arvin K. George*, Daniel M. Moreira*, Manaf Alom*, Zhamshid Oshunor*, Simo Solami*, Nikhil Wangwankar*, Michael J. Schwartz*, Manish A. Vira*, Lee Richtstone* and Louis R. Kavoussi*

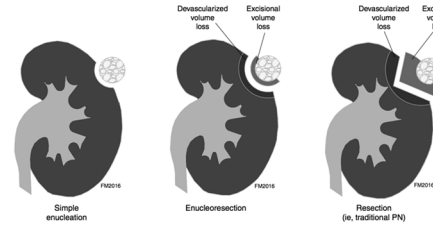
- 209 on-clamp; 106 off clamp
- Median f/u 2 years
- On clamp tumors a bit smaller (3.0 vs 3.4 cm) and more likely to be endophytic
- No difference in EBL or margin status
- significantly greater decrease in immediate postoperative renal function with hilar clamping
- ...the on-clamp group showed restoration of global renal function by 6 months, which endured with long-term follow-up
- ** No significant differences in postoperative eGFR were identified between clamping groups in either uni- or multivariable analysis of all comers **

From BJU Int 2015



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Standard resection vs Enucleation vs minimum margin PN



From Marconi et al Europ Urol Focus 2016

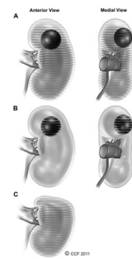
Fig. 3 - Resection techniques and parenchymal volume loss. PN = partial nephrectomy.



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Role of resected kidney tissue in recovery of renal function

- Lane et al evaluated 660 solitary kidneys after partial nephrectomy and found the 'quantity of kidney preserved', which was estimated at the time of surgery, and the preop GFR were the most important predictors of acute kidney injury after partial nephrectomy. (J urol 2011;185:421-7)
- Other groups have used MAG3 scans and CT volume measurements to more accurately determine volume saved after PN showing ultimate function after PN primarily correlated with parenchymal preservation and ischemia played a lesser role (Mir et al. Urology 2013, Zargar et al BJUI 2015)



© 2011

From Mir et al Urology 2013



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Positive surgical margins and local recurrence after simple enucleation and standard partial nephrectomy for malignant renal tumors: systematic review of the literature and meta-analysis of prevalence

Andrea MONTAUDO*, Riccardo CANNI*, Francesco MISA*, Ilham BERRAJOUI*, Giulio R. BIANCHI*, Andrea MONTAUDO*, Marco B. BIANCHI*, Massimo MELLA*, Alessandro VULPI*, Marco CANNI*, Robert U. VUJOVICH*

- Meta-analysis 33 studies, >11000 patients
- PSMs, Local-regional recurrence, renal recurrence
- PSM:
 - Enucleation: 2.7% (95% CI: 1.5-4.6%, P<0.001)
 - Standard PN: 0.4% (95% CI: 0.1- 2.2%, P=0.018)
- Simple enucleation was non-inferior to standard PN after minimum f/u 24 mos.

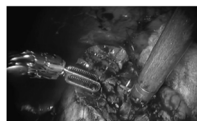
Minerva Urologica e Nefrologica 2017 December;69(6):523-38



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Laparoscopic/Robotic Partial Nephrectomy Techniques: Renorrhaphy

- Suturing base of resection bed
- With or without fibrin bolsters or other hemostatic agents?
 - No increased risk of bleeding with or without use of hemostatic agents at the time of Robotic PN (Maurice et al J Endourol 2016, Peyronnet World J Urol 2015)



From Sammon et al J Endourol 2011



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Laparoscopic/Robotic Partial Nephrectomy Techniques: Renorrhaphy

- Re-approximation of cortical edges – renorrhaphy
 - Running closure with or without barbed suture
 - Sliding clip renorrhaphy



From Sammon et al J Endourol 2011

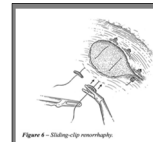


Figure 4 - Sliding clip renorrhaphy

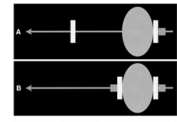


Fig. 1 Illustration of renorrhaphy with a Prolene suture. A RT view with a laparoscopic clip and a work clip on one side of the kidney. A second work clip is placed and will be slid down to the kidney with a robotic needle driver. B After sliding down the work clip, a second laparoscopic clip is placed on the other side.

From Sharyari et al. J Robotic Surg 2008



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Conclusions

- Vast majority of kidney cancer cases can be approached either laparoscopically or robotically with appropriate training and experience
- Modifiable risk factors for CKD include WIT and amount of kidney parenchyma lost after PN
- Advanced techniques in experienced hands include robotic IVC thrombectomy and super selective clamping for PN
- NOTES and LESS are still exploratory and await improved technology prior to more widespread application
- Hemostatic agents during robotic partial nephrectomy do not reduce bleeding risk

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Kidney Cancer – Systemic Therapy for Advanced Disease

David McDermott, MD
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Dana-Farber/Harvard Cancer Center

Disclosures

Consultant

- Array Biopharma
- Bristol-Myers Squibb
- Calithera Biosciences
- Exelixis
- Genentech
- Merck
- Novartis
- Pfizer

Research funding

- Prometheus Labs
- Bristol-Myers Squibb

2

Kidney Cancer: Epidemiology

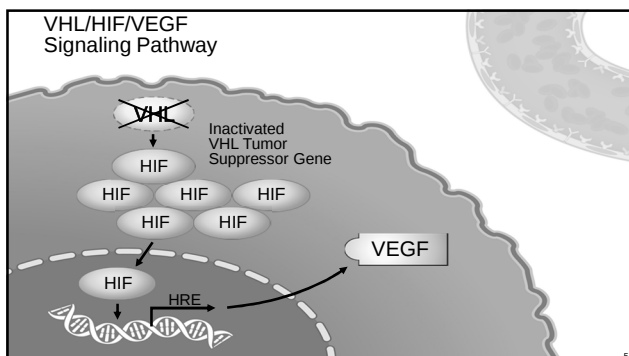
- U.S. New cases/deaths* 63,340/14,970
- % of all cancers/ deaths 2.5% / 2%
- Male predominance 3:2
- Median age ~64
- Smoking and obesity are known risk factors
- Incidental findings increasing
- Stage: local 60-70%
- regional 5-10%
- metastatic 15-20%

40% will eventually develop Stage IV disease

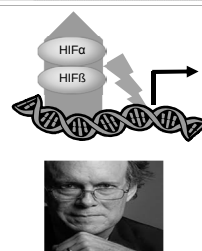
*American Cancer Society, 2018

Where are the best targets in Advanced RCC?

- One answer: the vHL Pathway
- Why?
 - Tumor suppressor gene
 - Commonly inactivated in clear cell RCC (70%)
 - Inactivation induces hypoxia-regulated genes
 - Promoting angiogenesis and tumor growth



The HIF Transcription Factor



- Glucose Uptake (e.g. GLUT1)
- Anaerobic Glycolysis (e.g. PFK, LDH)
- Angiogenesis (e.g. VEGF, PDGF, IL-8, TGFβ)
- Erythropoiesis (e.g. EPO*)
- Invasion/Homing (e.g. MMP2, MMP9, c-MET, CXCR4)
- Mitogenesis (e.g. TGFα, Cyclin D1*)

DF/HCC

* Tissue specific

6

Metastatic Clear-Cell RCC (mRCC): 12+ Years of Impressive Progress

Setting	NCCN ^a	Alternative
1st-Line Therapy	Good or intermediate risk	Sunitinib Pazopanib Bevacizumab + IFN α
	Poor risk	Temsirolimus
2nd-Line Therapy	Prior VEGFR inhibitor	Cabozantinib Nivolumab Axitinib Everolimus/Lenvatinib
		Clinical Trials

^aCategory 1 recommendations unless noted; NCCN Guidelines, Kidney Cancer, V.2.2018; ^bCategory 2A; ^cintermediate/poor risk

mRCC: Standard of Care 2017*

Setting	NCCN	Alternative
1st-Line Therapy	VEGF Blockade	
2nd-Line Therapy	Prior VEGFR inhibitor	Cabozantinib Nivolumab Axitinib Everolimus/Lenvatinib
		Clinical Trials

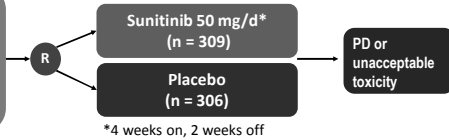
*Motzer et al NEJM, 2007; Sternberg et al JCO 2010; Motzer et al NEJM 2013

Adjuvant Sunitinib in High-Risk RCC

S-TRAC Study

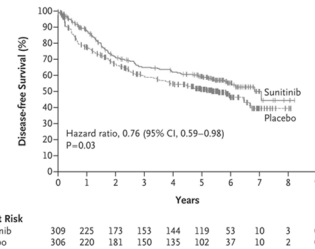
- Randomized, double-blind, placebo controlled phase 3 trial

Patients with locoregional, high-risk clear cell RCC post-nephrectomy (N = 615)



Primary endpoint: DFS

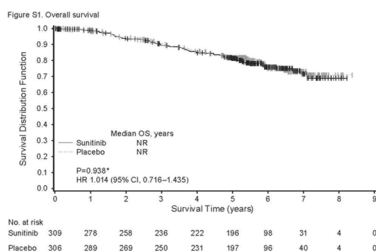
Ravaud A, et al. *N Engl J Med*, 2016.



S-TRAC: Adjuvant sunitinib versus placebo

- One year of adjuvant therapy, one year of disease-free survival benefit
- Sunitinib toxicities similar to those encountered in metastatic setting

Ravaud A et al NEJM 2016 375(23):2246-54.



S-TRAC: Adjuvant sunitinib versus placebo

- No hint of a survival benefit although OS results preliminary
- Should we be using TKIs at this point, or is there a better way?

Ravaud A et al NEJM 2016 375(23):2246-54.

Why do we not see a survival difference with VEGFR TKIs?

- ✓ Analysis is too early for OS
- ✓ Biology of the disease

What would I need to change my mind on VEGFR-TKI adjuvant therapy?

- ✓ Mature OS data from S-TRAC and ASSURE
- ✓ Further results from SORCE, PROTECT, and ATLAS
- ✓ Positive meta-analysis of VEGFR-TKI adjuvant studies

On the horizon: Adjuvant immunotherapy

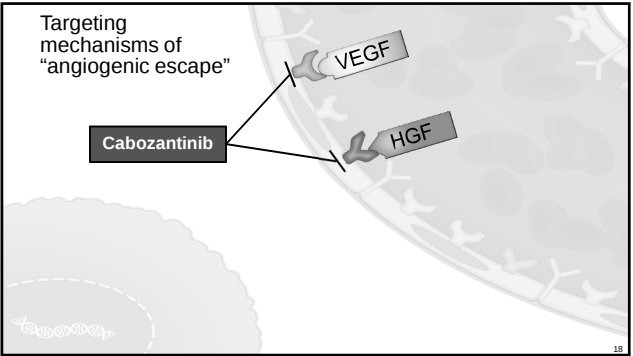
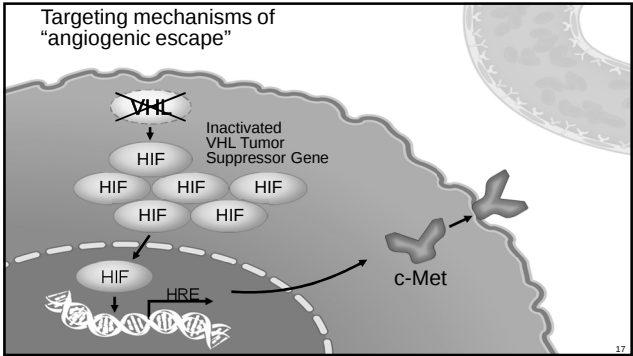
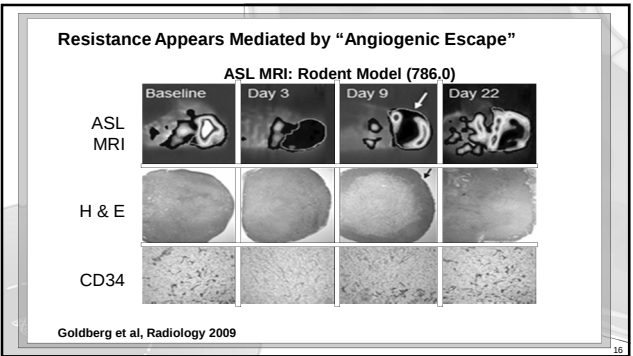
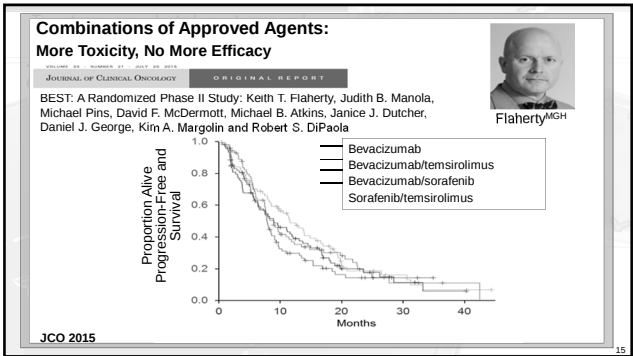
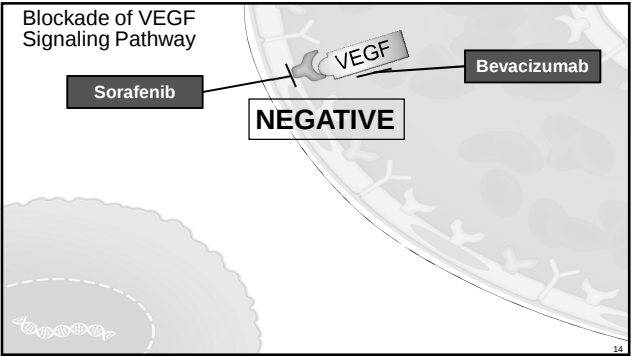
ORIGINAL ARTICLE

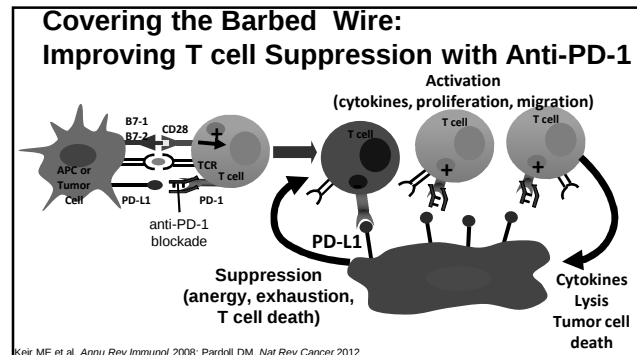
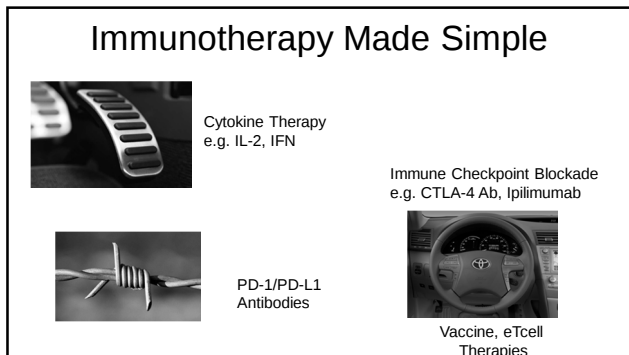
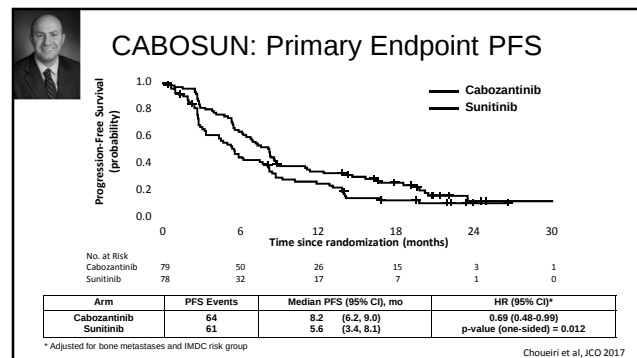
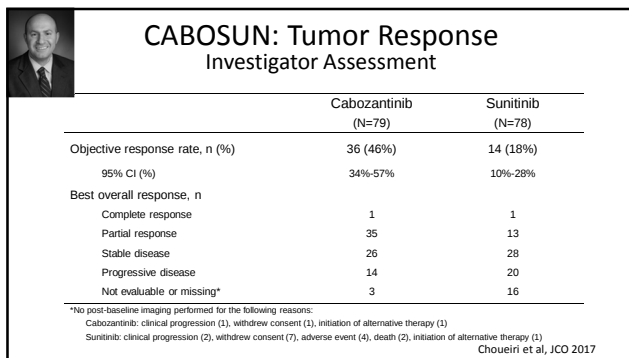
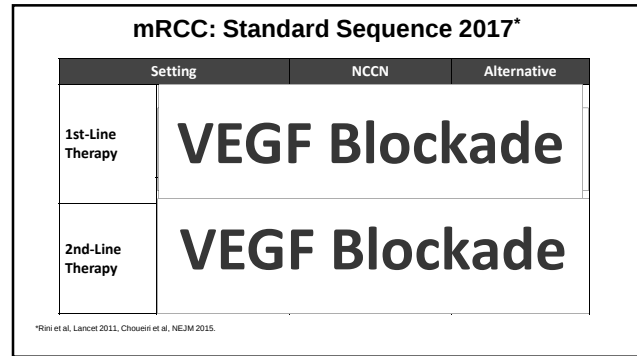
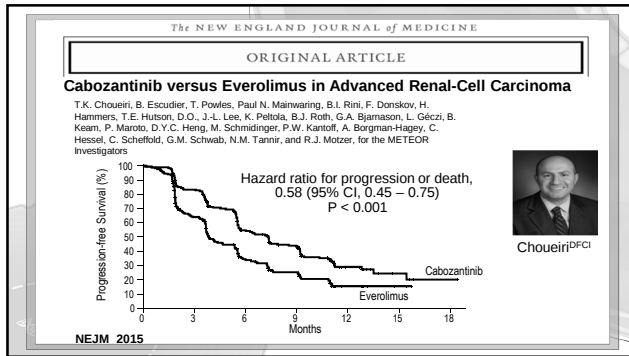
Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

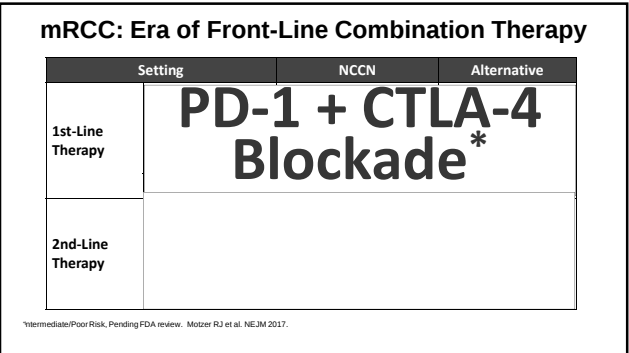
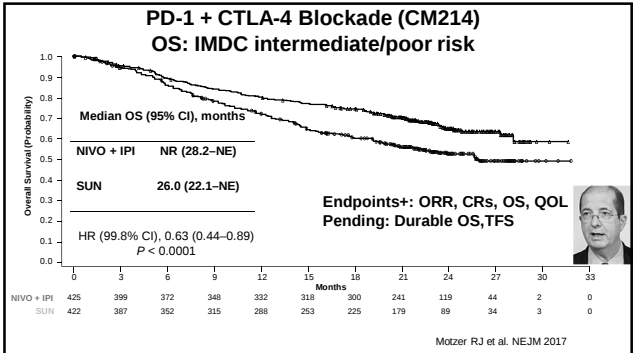
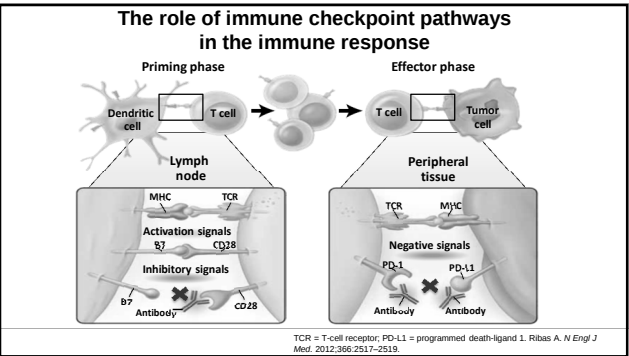
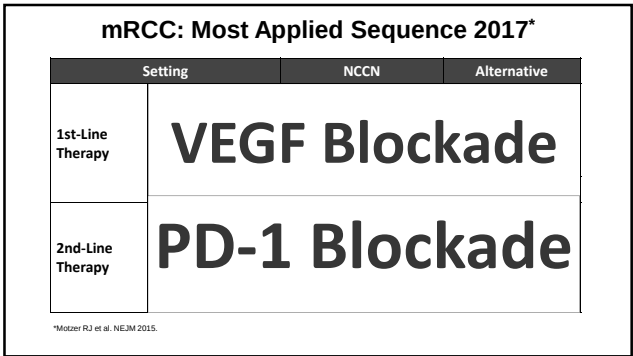
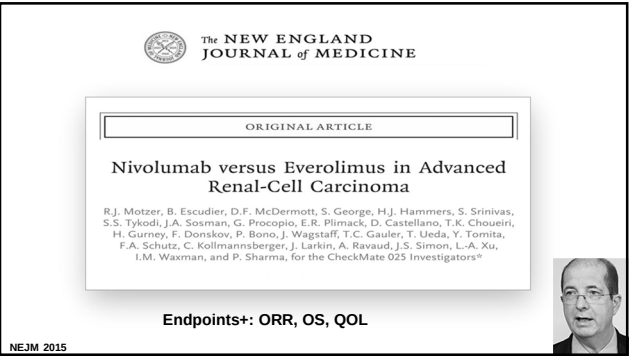
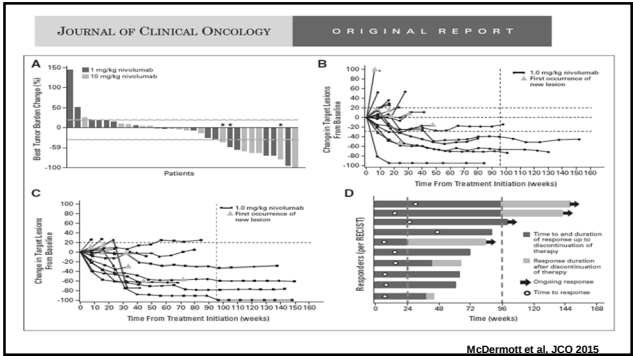
A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thierry-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linossier, E. Lechevallier, C. Besland, M. Atchison, S. Oudard, J.-J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.-C. Bernhard, L. Albiges, M.-O. Timsit, T. Lebre, and B. Escudier

PRESENTED AT: 2018 ASCO ANNUAL MEETING

PRESENTED BY: Arnaud Méjean







Exploratory endpoint ORR and PFS: IMDC favorable risk

Outcome	N = 249 ^a	
	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR, ^b % (95% CI)	29 (21–38)	52 (43–61)
P = 0.0002		
PFS, ^c median (95% CI), months	15.3 (9.7–20.3)	25.1 (20.9–NE)
HR (99.1% CI) 2.18 (1.29–3.68)		
P < 0.0001		

MAURO
2017

ESMO CONGRESS
^a11% of patients in both arms had tumor PD-L1 expression ≥10%
^bORR assessed by RECIST v1.1
^cPFS assessed

Immune-mediated adverse events: All treated patients

Category, %	NIVO + IPI N = 547	
	Any grade	Grade 3–4
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis and renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion reaction	1	0
Hypothyroidism	19	<1
Hyperthyroidism	12	<1
Adrenal insufficiency	8	3
Hypophysitis	5	3
Thyroiditis	3	<1
Diabetes mellitus	3	1

- 35% of patients treated with NIVO + IPI required systemic HD corticosteroids for an adverse event
- Secondary immunosuppression with infliximab (3%) and mycophenolic acid (1%) was reported

Immune-mediated AE analyses included events, regardless of causality, occurring <100 days of the last dose. These analyses were limited to patients who received immune modulating medication for treatment of the event, except endocrine events that were included in the analysis regardless of treatment since these events are often managed without immunosuppression.

Will Cost Impact Access to Therapy?: Lessons from Melanoma

Regimen cost for “typical” patient (80 kg) with
Melanoma in Phase 3 (Checkmate 067)^a

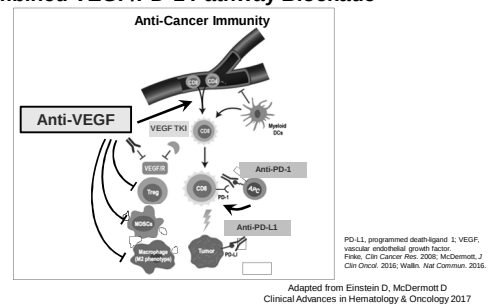
Drug	Median Doses	Cost
Nivolumab	15	\$89,000
Nivolumab + ipilimumab	4	\$150,000
Remission	0	0

- Nivolumab: \$24.70/mg^b
- Ipilimumab: \$135.18/mg^b

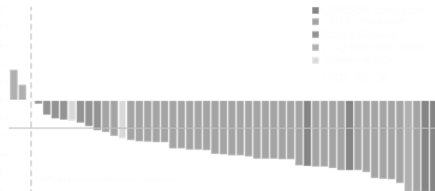
^aLarkin J et al. *N Engl J Med*. 2015; 373:23–34.

^bFirst quarter 2016, in US dollars.

Shifting the Balance Toward Anti-Cancer Immunity With Combined VEGF/PD-1 Pathway Blockade



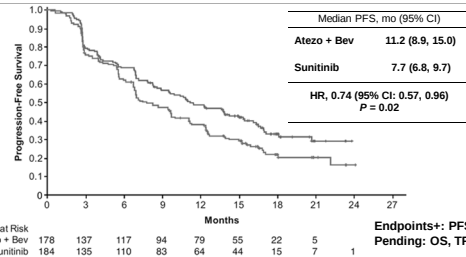
VEGF TKI + PD-1 Ab: Tumor Response



* Stable disease or partial response not confirmed, or no follow-up scans available.
ORR=objective response rate

Presented by: Michael B Atkins, MD Lancet Oncology 2018

Anti-PD-L1/VEGF Antibodies (IM151) Progression-Free Survival in PD-L1+



PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo. The PFS analysis passed the pre-specified P-value boundary of alpha = 0.04.

Motzer RJ et al. GU ASCO 2018. Abst 578

mRCC: Most Applied Sequence 2018^c

Setting	NCCN ^a	Alternative
1st-Line Therapy	VEGF Blockade	
2nd-Line Therapy	PD-1 Blockade	

^aCategory 1 recommendations unless noted; NCCN Guidelines, Kidney Cancer, V 2.2018. ^bCategory 2A, ^cintermediate/poor risk. Motzer RJ et al. NEJM 2015.

mRCC: Fusion of First and Second-line Therapy

Setting	NCCN ^a	Alternative
Treatment Naive	PD-1 + VEGF Blockade ^d	
3rd-Line Therapy		

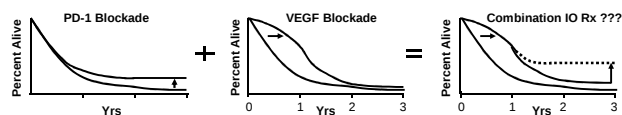
^aCategory 1 recommendations unless noted; NCCN Guidelines, Kidney Cancer, V 2.2018. ^bCategory 2A, ^cintermediate/poor risk. ^dPending FDA review. Motzer RJ et al. SITC 2016, Abstract 038. ^eMotzer et al. GU ASCO Abstract.

First-Line PD-1 Based Combination Phase 3 Trials in mRCC

Control	Experimental Arm
Sunitinib	Axitinib + avelumab
Sunitinib	Bevacizumab + atezolizumab
Sunitinib	Nivolumab + cabozantinib or nivolumab + ipilimumab + cabozantinib
Sunitinib	Lenvatinib + everolimus or lenvatinib + pembrolizumab
Sunitinib	Axitinib + pembrolizumab
Sunitinib	Nivolumab + ipilimumab ✓

Are these approaches additive or synergistic?

PD-1 Blockade Based Combinations in mRCC: Are they Additive or Synergistic?



- PD-1 + VEGF **certainly** additive
 - ORR and mPFS outcomes are encouraging
 - But are these combination synergistic?
 - Will they produce a plateau on the PFS curve? Or durable OS? Can you stop the Rx?
- Synergistic benefits will generate improvement in IO* endpoints
 - e.g. Long Term OS, remissions, CR or near-CR

IO – Immunology, Side courtesy of T Ribas.

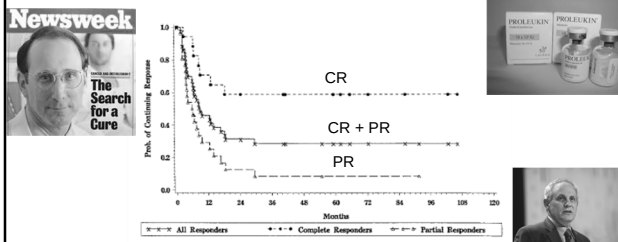
mRCC PD-1 Based Combination Trial Summary*

	Atezo + Bev ¹ IMmotion151		Nivo + Ipi ² CheckMate 214	
	PDL1+	ITT	I/p	ITT
Phase	3		3	
Comparator	Sunitinib		Sunitinib	
N	178	454	425	550
Median follow-up, months	15	11.2	11.6 ¹	25.2
mPFS, months	11.2	11.2	11.6 ¹	12.4 ¹
mOS, months (95% CI)	NR	NR	NR (28.2-NE)	NR
HR (95% CI)	0.68 (0.46, 1.00)	0.81 (0.63, 1.03)	0.63 (0.44, 0.89) ²	0.68 (0.46, 0.95) ²
ORR, %	43	37	42 ¹	39 ¹
CR, %	9	5	9	NA
All-cause AEs, %	NA		NA	
TRAEs, %	NA		NA	
All grades/Grade 3 or 4	NA		NA	
Discontinuations due to AEs/TRAEs, %	NA		NA	

*Data represent a summary of reported data and are not intended for cross-trial comparisons. ¹IRRC-assessed. ²Investigator-assessed. ³Data are considered immature. ⁴Includes all AEs ≥ grade 3. ⁵Range is 99.8% confidence interval.

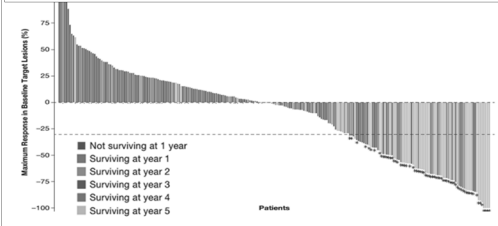
1. Motzer et al. GU ASCO 2016. 2. Escudier, et al. Presented at: ESMO 2017, Abstract LB45.

Proof of Principle: Deep responses produce remissions



Atkins et al. J Clin Oncol. 1999

Deep Responses = Durable Survival Target Tumor reduction and length of survival with PD-1 blockade (CM-003)



*Includes all patients with target lesion at baseline and ≥1 on-treatment tumor assessment. Asterisks in waterfall plot represent responders (ie, achieved a partial response or complete response).
Devices changes truncated at 100%.
CR = complete response; ORR = objective response rate; PR = partial response; SD = stable disease.

Topalian et al, # P216 SITC 2017

First-Line Phase 3 Trials in Advanced RCC

Control	Experimental Arm
Sunitinib	Axitinib + avelumab
Sunitinib	Bevacizumab + atezolizumab
Sunitinib	Nivolumab + cabozantinib or nivolumab + ipilimumab + cabozantinib
Sunitinib	Lenvatinib + everolimus or lenvatinib + pembrolizumab
Sunitinib	Axitinib + pembrolizumab
Sunitinib	Nivolumab + ipilimumab

Should these approaches be applied to all patients?

How do we combine therapies to improve IO outcomes?



Slide courtesy of R. Sullivan, MGH

First-Line PD-1 Based Combination Phase 3 Trials in mRCC

- Important Unanswered Questions:
 - Are benefits outweighed by costs?
 - Is combination > sequence?
 - PD-1 + X > VEGF
 - But is PD-1 + X > VEGF followed by PD-1?
 - Not well studied yet
 - What is the activity of PD-1 Blockade in first-line?

Nivo P3 Trial: Antitumor activity

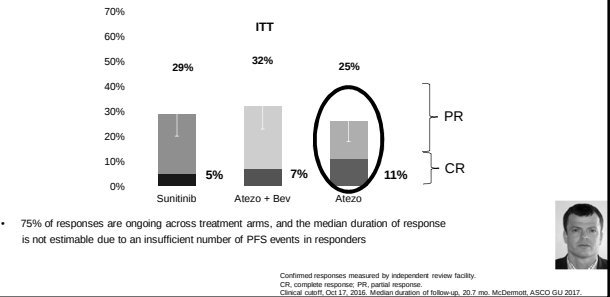
	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)	12.0 (0–27.6+)	12.0 (0–22.2+)
Ongoing response, n/N (%)	45/103 (44)	8/22 (36)

Advanced Clear Cell RCC: Ten+ Years of Impressive Progress

Setting	NCCN ^a	Alternative
1st-Line Therapy	Sunitinib	
	Nivolumab + Ipilimumab	
2nd-Line Therapy	Poor risk*	Temsirolimus
	Prior VEGFR inhibitor	Cabozantinib, Nivolumab, Axitinib, Everolimus/ Lenvatinib

*Category 1 recommendations unless noted in parentheses: NCCN Guidelines: Kidney Cancer, V.2.2018

Immotion 150: 1L PD-L1 Blockade Overall Response Rate

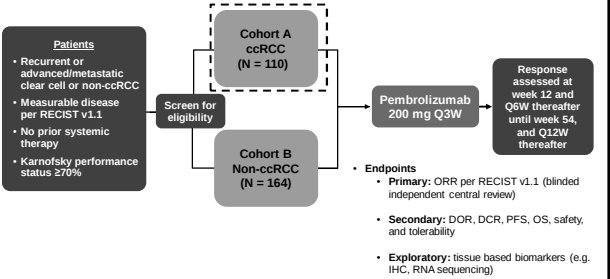


Pembrolizumab Monotherapy as First-Line Therapy in Advanced Clear Cell Renal Cell Carcinoma: Results From Cohort A of KEYNOTE-427

D. F. McDermott¹, J.-L. Lee², C. Szczylik³, F. Donskov⁴, J. Malik⁵, B. Y. Alekseev⁶, J. M. G. Larkin⁷, V. B. Matveev⁸, R. A. Gafanov⁹, P. Tomczak¹⁰, S. S. Tykodi¹¹, P. F. Geertsens¹², P. Wiechno¹³, S. J. Shin¹⁴, F. Pouliot¹⁵, T. A. Gorda¹⁶, W. Li¹⁷, R. F. Perini¹⁸, C. Schloss¹⁹, M. B. Atkins¹⁹

¹Dana-Farber/Harvard Cancer Center, Boston, MA, USA; ²Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea; ³Mogkowsky Instytut Medyczny, Warszawa, Poland; ⁴Aarhus University Hospital, Aarhus, Denmark; ⁵Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK; ⁶P. A. Herzen Moscow Oncology Research Institute, Ministry of Health of the Russian Federation, Moscow, Russian Federation; ⁷Institute of Cancer Research, London, UK; ⁸N. N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation; ⁹Russian Scientific Center of Roentgenradiology, Moscow, Russian Federation; ¹⁰Clinical Hospital No. 1 of the Pomeranian University of Medical Sciences, Pomeranian, Poland; ¹¹University of Washington Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ¹²Herlev Hospital, University of Copenhagen, Herlev, Denmark; ¹³Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland; ¹⁴Pomona University College of Medicine, Seoul, Republic of Korea; ¹⁵Université Laval, Québec, QC, Canada; ¹⁶Hospital Universitario Ramón y Cajal, Madrid, Spain; ¹⁷MSD China, Beijing, China; ¹⁸Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁹Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA

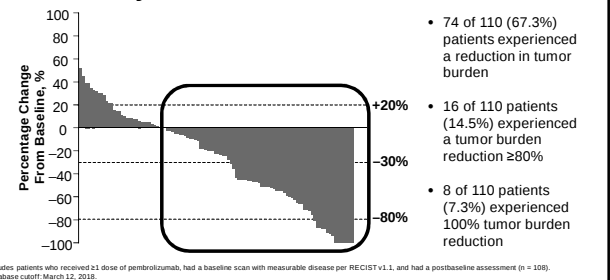
KEYNOTE-427: (NCT02853344)



Confirmed ORR by Blinded Independent Central Review

	N = 110		
	n	%	95% CI
ORR	42	38.2	29.1-47.9
DCR (CR + PR + SD ≥6 months)	65	59.1	49.3-68.4
Best overall response			
CR	3	2.7	
PR	39	35.5	
SD	35	31.8	
PD	31	28.2	
No assessment	2	1.8	

Maximum Change From Baseline in Target Lesions by Central Review



Treatment-Related Adverse Events

n (%)	Any Grade (≥5% of pts)	n (%)	Grade 3/4 (≥2 pts)
N = 110		N = 110	
Any	88 (80.0)	Any	24 (21.8)
Pruritus	30 (27.3)	Diarrhea	4 (3.6)
Fatigue	27 (24.5)	Colitis	3 (2.7)
Diarrhea	21 (19.1)	Asthenia	2 (1.8)
Rash*	17 (15.5)	Hepatitis	2 (1.8)
Arthralgia	14 (12.7)	AST increased	2 (1.8)
Hypothyroidism	11 (10.0)	Hyponatremia	2 (1.8)
ALT increased	8 (7.3)	Hypophosphatemia	2 (1.8)
AST increased	8 (7.3)		
Asthenia	7 (6.4)		
Decreased appetite	7 (6.4)		
Dry mouth	7 (6.4)		
Infectious illness	6 (5.5)		

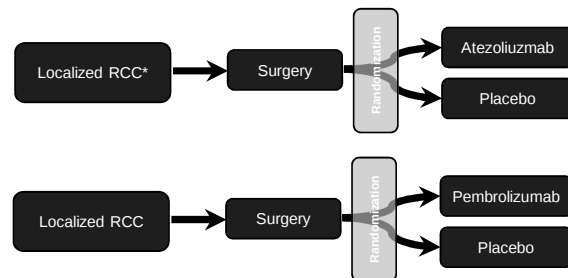
*Includes rash, rash maculopapular, and rash macular.
*40 mg prednisone or equivalent/day.
Database cutoff: March 12, 2018.

- Discontinuation because of a treatment-related AE was reported in 12 (10.9%) patients
- High dose steroids* were administered in 14 patients (12.7%)
- 1 patient had grade 5 treatment-related pneumonitis

Conclusions

- Pembrolizumab has shown promising antitumor activity as monotherapy in first-line ccRCC across IMDC risk groups, with ORR 38%
 - Encouraging activity was also observed in key subgroups, such as IMDC intermediate/poor risk (ORR, 42%) and patients with PD-L1-positive tumors (ORR, 50%)
 - ORR of 32% in patients with IMDC favorable risk
- Safety profile in KEYNOTE-427 cohort A was similar to the previously described safety profile of pembrolizumab in other tumor types
- Cohort B of KEYNOTE-427, to explore the role of pembrolizumab monotherapy in non-ccRCC patients, is ongoing
- Results presented herein provide support for the exploration of pembrolizumab in the adjuvant setting (KEYNOTE-564 NCT03142334, currently enrolling) and will allow investigators to put the benefit of anti-PD-1-based combination therapies in better context

Kidney Cancer Adjuvant Therapy Trials: Is Selection Possible?



Phase 3 Trials Assessing Adjuvant Immunotherapy for High-risk Localized RCC¹

Treatment Arms	Primary Endpoint	Trial	ClinicalTrials.gov ID
Atezolizumab vs Placebo	DFS	IMmotion010	NCT03024996
Pembrolizumab vs Placebo	DFS	KEYNOTE-564	NCT03142334
Neoadjuvant nivolumab → Surgery → adjuvant nivolumab vs observation	RFS	PROSPER RCC	NCT03055013
Nivolumab + ipilimumab vs placebo	DFS	CHECKMATE 914	NCT03138512
Durvalumab vs durvalumab + tremelimumab vs active surveillance	DFS and OS	RAMPART	NCT03288532

1. <https://www.clinicaltrials.gov>. Accessed May 6, 2018.

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

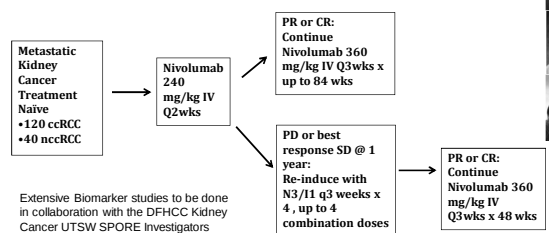
NEJM, 2016

Rational Application of Combination IO Therapy:

- Trial Design**
 - Sequence and Combination Comparisons
 - e.g. PD-1/CTLA-4 vs PD-1/VEGF
 - Flexible Combinations**
 - Can you build on single agent PD-1?
 - What happens when you stop rx?
- Patient Selection**
- Novel Endpoints**

PD-1 then CTLA-4 Blockade

Trial Diagram – HCRN GU 260 (BMS 209-669)



Extensive Biomarker studies to be done in collaboration with the DFHCC Kidney Cancer UTSW SPORE Investigators

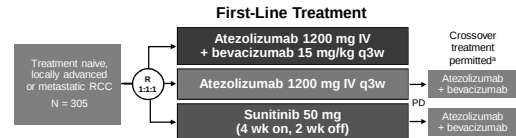
Opened 4/17/17

Atkins, Hammers, Signoretti
NCT03117309

Rational Application of Combination IO Therapy:

- Trial Design
- Patient Selection
- Novel Endpoints

IMmotion150 (Phase II) Trial Design

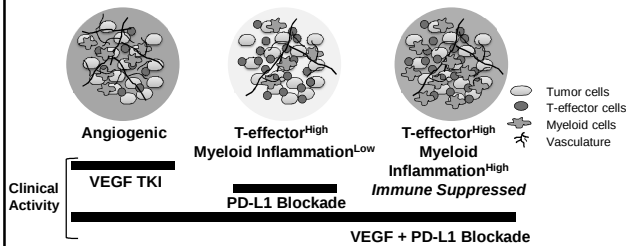


- IMmotion150 was designed to be hypothesis generating and inform the Phase III study IMmotion151
- Coprimary endpoints were PFS (RECIST v1.1 by IRF) in ITT patients and patients with $\geq 1\%$ of IC expressing PD-L1
- Exploratory endpoints included interrogation of the association between outcome and TME gene signatures

IC, tumor-infiltrating immune cells; IRF, independent review facility; ITT, intention-to-treat; TME, tumor microenvironment. *Crossover from atezolizumab monotherapy not allowed in Europe. McDermott, JCO 2018; McDermott, ASCO GU 2017.

McDermott D, et al. IMmotion150 biomarkers: Nature Med 2018

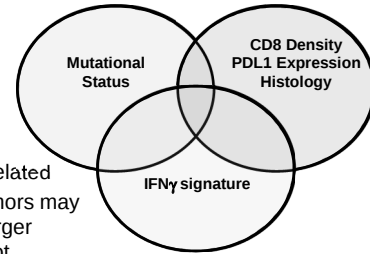
Immotion 150: Molecular Correlates of Differential Response in mRCC



McDermott D, et al. IMmotion150 biomarkers: AACR 2017

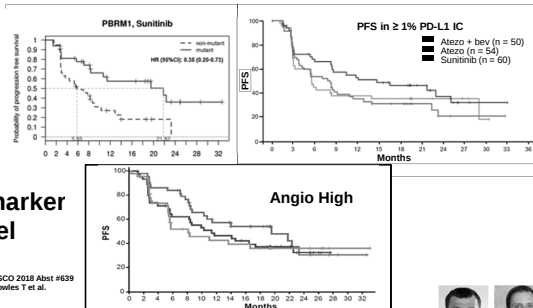
Biomarker Model

- All inter-related
- Some tumors may have a larger sweet spot



M Atkins with permission.

Biomarker Model



Voss et al GU ASCO 2018 Abst #639
McDermott D, Powles T et al.
AACR 2017



Rational Application of Combination IO Therapy:

- Trial Design
- Patient Selection
- Novel Endpoints
 - Make IO Endpoints Primary
 - Speed R&D
 - Achieve patient's goal

Established Landmark Endpoints: CWG HD IL-2 Phase 3 Trial

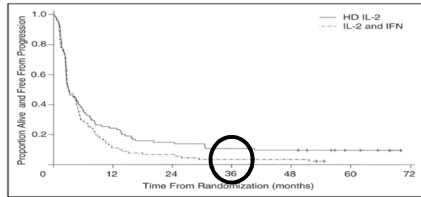


Fig 2. Progression-free survival by treatment arm among 186 patients receiving high-dose interleukin-2 (HD IL-2; n = 95) or receiving IL-2 and interferon alpha-2b (IFN; n = 91). Ten patients receiving HD IL-2 remained progression-free at 3 years compared with three patients who received IL-2 and IFN (P = .082 by Fisher's exact test).

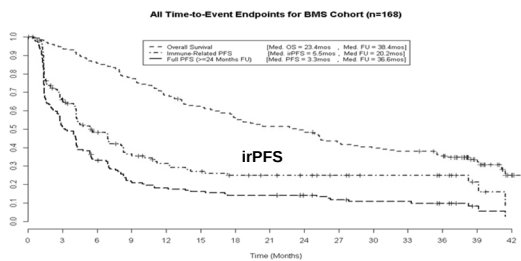
McDermott et al, JCO 2005

The Future of Immunotherapy

- **Combination therapy based on pre-clinical models**
 - Freeman^{DFCI}/Sharpe^{HMS} PIs
 - NeoVax - Choueiri/Wu^{DFCI} PIs
- **Front-line/Adjuvant therapy**
 - PROSPER (Nivo) – Harshman^{DFCI} PI
 - Atezo – Pal^{COH}, Uzzo^{FCCC} – PIs
 - Pembro – Choueiri^{DFCI} – PI
- **Predictive biomarker development**

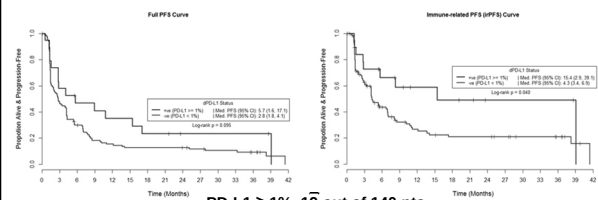


Impact of Immune Endpoints on PFS outcome of 010 Study



Pignon et al GU ASCO 2018 #619

irPFS may improve ability to predict IO response PD-L1 expression on tumor cells is associated with longer irPFS (CM010)



PD-L1 ≥ 1%, 19 out of 140 pts
PD-L1 < 1%, 121 out of 140 pts

Pignon et al GU ASCO 2018 #619



Conclusions

Rational application of sequential Rx in RCC:

- FDA Support for:
 - Innovative Trial Design
 - IO Endpoints
 - Next Gen Biomarkers
- Focus on the Patient's Goal:
 - Increasing Treatment-free Survival

Standard Therapy for mRCC: 2028

Setting	NCCN	Alternative
1st-Line Therapy	Treatment based on TME* Profile	
2nd-Line Therapy	Not Necessary	

*TME – Tumor Microenvironment, Smyth et al, Nat Rev Clin Oncol 2016

Acknowledgements

- Participating study investigators and clinical sites
- The Immotion 150/151 studies were sponsored by F. Hoffmann-La Roche, Ltd, Checkmate 214 by Bristol-Myers Squibb, Keynote 427 by Merck
- Genentech Translational Team
 - Mahrukh Huseni, Priti Hegde
- DF/HCC KCP SPORE Colleagues

Ablative Therapies in Management of Renal Cell Carcinoma

Rus Korets, MD
Division of Urology
Beth Israel Deaconess Medical Center



Disclosures

- No financial disclosures
- No conflicts of interest

Learning Objectives

- Discuss minimally invasive treatment options for small renal masses
- Review mechanism of action, surgical techniques, and complications of ablative therapies
- Review oncologic outcomes and follow-up protocols after tumor ablation

Estimated New Cases

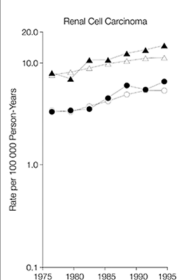
	Males	Females
Prostate	164,690 19%	Breast 286,120 30%
Lung & bronchus	121,680 14%	Lung & bronchus 112,350 13%
Colon & rectum	75,610 9%	Colon & rectum 64,640 7%
Urinary bladder	62,360 7%	Uterine corpus 63,230 7%
Melanoma of the skin	56,150 6%	Thyroid 40,900 5%
Kidney & renal pelvis	42,680 5%	Melanoma of the skin 36,120 4%
Non-Hodgkin lymphoma	41,730 5%	Non-Hodgkin lymphoma 32,950 4%
Oral cavity & pharynx	37,160 4%	Pancreas 26,240 3%
Leukemia	35,030 4%	Leukemia 25,270 3%
Liver & intrahepatic bile duct	30,610 4%	Kidney & renal pelvis 22,680 3%
All Sites	856,370 100%	All Sites 676,950 100%

Estimated Deaths

	Males	Females
Lung & bronchus	83,550 26%	Lung & bronchus 70,500 25%
Prostate	29,430 9%	Breast 40,920 14%
Colon & rectum	27,360 8%	Colon & rectum 23,240 8%
Pancreas	23,020 7%	Pancreas 21,310 7%
Liver & intrahepatic bile duct	20,540 6%	Ovary 14,070 5%
Leukemia	14,270 4%	Uterine corpus 11,350 4%
Esophagus	12,850 4%	Leukemia 10,100 4%
Urinary bladder	12,520 4%	Liver & intrahepatic bile duct 9,660 3%
Non-Hodgkin lymphoma	11,510 4%	Non-Hodgkin lymphoma 8,400 3%
Kidney & renal pelvis	10,570 3%	Brain & other nervous system 7,340 3%
All Sites	323,650 100%	All Sites 286,610 100%

Cancer statistics, 2014, Volume 64, Number 4, Pages 7-30, First published 5th January 2014, DOI: 10.3322/caac.21449

Background



- Incidence of renal masses has increased due to surge in routine use of CT
 - RCC incidence rising by 3%/yr
 - Many of the tumors are incidentally discovered and small in size (~66%)
- Cancer-specific mortality remains relatively unchanged
 - Many small masses may be treated too aggressively

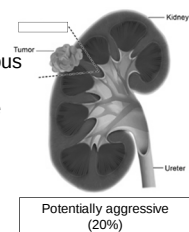
Hollingsworth, J NCI 2006
Chow, Cancer 2008

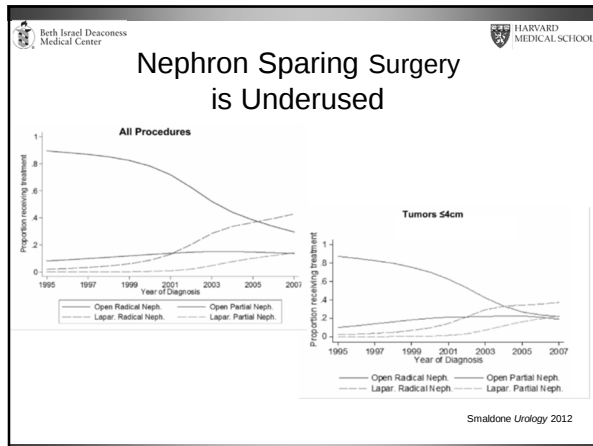
Siegel CA Cancer J Clin 2018

The Small Renal Mass Dilemma

- Small renal mass (SRM):

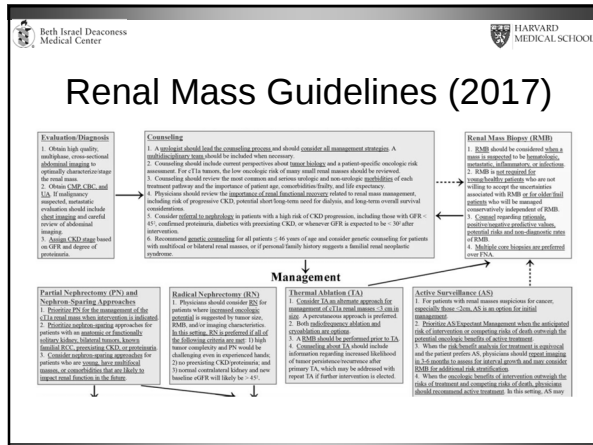
- Typically defined as small (<4cm), solid, organ confined tumor suspicious for RCC
- Partial nephrectomy continues to be 'gold standard'
 - Improved preservation of renal function
 - Superior cardiac outcomes





Background

- Small renal mass (SRM)
 - Typically defined as small (<4cm), solid, organ confined tumor suspicious for RCC
 - Partial nephrectomy continues to be 'gold standard'
- Alternative treatment options
 - Thermal Ablation
 - Active surveillance



Pre-procedural Evaluation

- Medical evaluation
 - INR < 1.5
 - Platelet count > 50,000/uL
- Labs:
 - INR < 1.5
 - Platelet count > 50,000/uL
- Cross-sectional imaging

Algorithm to Identify variables

- **A** - Axial tumor diameter
- **B** - Bowel proximity
- **L** - Location within kidney
- **A** - Adjacency to the ureter
- **T** - Touching renal sinus fat
- **E** - Endo/exophytic

Schmitz et al AJR 2014

Pre-procedural Biopsy

- Performed as a separate procedure or immediately prior to ablation
- Guides frequency and length of follow-up imaging

Size	Malignant	Benign
0 - < 1 cm	43 (64%)	37 (46%)
1 - < 2 cm	132 (78%)	38 (22%)
2 - < 3 cm	266 (78%)	75 (22%)
3 - < 4 cm	285 (80%)	71 (20%)
All sizes (0-4 cm)	726 (77%)	221 (23%)

Adapted from Franks et al. J Urol. 2003;170

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Treatment Options

- Cryoablation
- Radiofrequency ablation
- Microwave Ablation
- Irreversible Electroporation

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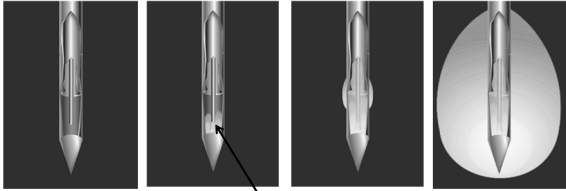
Cryoablation: Historical Perspective

- 2500 BC: Inflammatory disorders (Ancient Egypt)
- 1850: Ice + salt for cancer of Cervix and Breast (James Arnott)
- 1963: First modern cryoprobe using pressurized liquid nitrogen (Cooper and Lee)
- 1960's to 1980's: evolution of urologic application from open approaches to transurethral to transperineal.
- 1968: 1st renal cryosurgery (Lutzeyer and Lymberopulos)
- 1995: 1st percutaneous renal cryoablation (Uchida)



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Cryoablation Principles

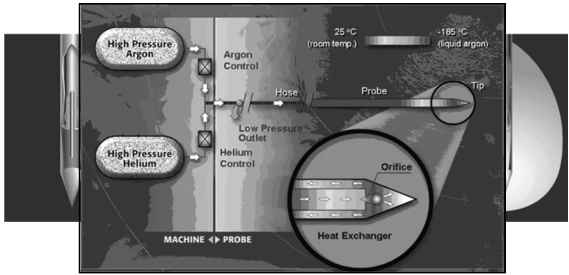


Argon gas expands through orifice

The Joule-Thompson Principle: Inert gases undergo unique temperature changes when depressurized. The expansion of argon at narrow terminal port results in rapid cooling (-185.7° C) at the tip of probe. Helium is used for heating (67° C)

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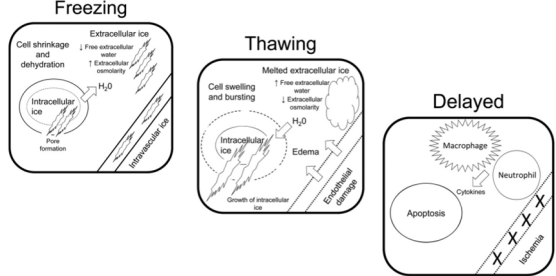
Cryoablation Principles



The Joule-Thompson Principle: Inert gases undergo unique temperature changes when depressurized. The expansion of argon at narrow terminal port results in rapid cooling (-185.7° C) at the tip of probe. Helium is used for heating (67° C)

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Mechanism of Action



Freezing

Thawing

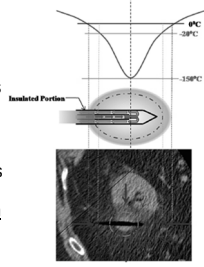
Delayed

Erinjeri, J Vasc Interv Radiol 2010

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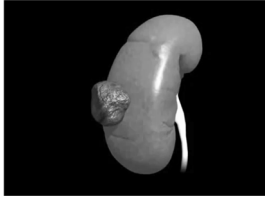
Treatment Temperature

- Dependent on cell type and cellular environment of target tissue
 - Normal renal parenchyma destruction occurs at -19.4°C
 - Renal Cell Carcinoma cellular death is achieved at -50°C
- Temperature within ice-ball is **not** uniform
 - The visible ice-ball margin demarcates the 0°C isotherm, which is not lethal
 - At least a **5-mm cryoablation margin** beyond the target is thought necessary to ensure target ablation



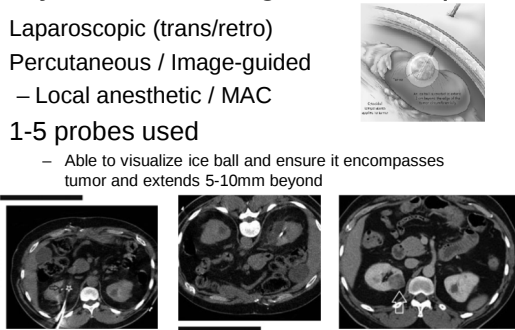
Freeze-Thaw Cycles

- Double freeze-thaw cycles are recommended to ensure cellular death
- Duration of treatment: 8-10 mins
- Passive vs Active thawing



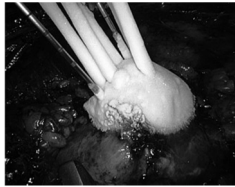
Cryoablation: Surgical Technique

- Laparoscopic (trans/retro)
- Percutaneous / Image-guided
 - Local anesthetic / MAC
- 1-5 probes used
 - Able to visualize ice ball and ensure it encompasses tumor and extends 5-10mm beyond



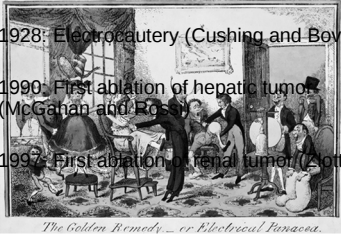
Key to Successful Cryoablation

- Proper monitoring of ablation
- Rapid cooling to lethal temperature
- Repetition of freeze-thaw cycle
- Slow thawing

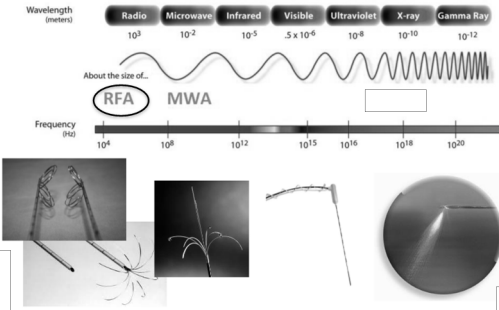


Radiofrequency Ablation

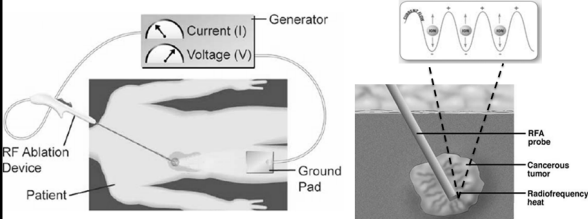
- 3000 BC: Ancient Egypt – cauterization of tumors
- 1900s: Medicated electricity
- 1928: Electrocautery (Cushing and Boyie)
- 1990: First ablation of hepatic tumor (McGahan and Ross)
- 1993: First ablation of renal tumor (Zotta)




Thermal Ablation: Principles



Radiofrequency Ablation: Principles

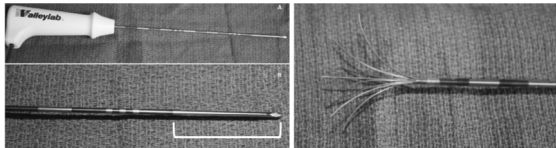


Tumor heated to 60° C - 100° C → cell death via coagulative necrosis in matter of minutes

- Monopolar current causes ionic agitation → frictional heating in surrounding tissue (i.e. no direct heating)
- Tissue desiccation increases impedance which eventually decreases current flow

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Radiofrequency Ablation: Principles



Kelly Int J Surg 2016

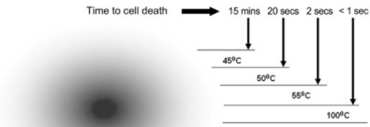
Effect of heat on tissue:

- 80°C - protein denaturation, coagulation
- 100°C: vaporization, dehydration, & tissue ablation
- 150-300°C: carbonization (limits further heat conduction)

- **Monitoring:**
 - Temperature
 - Impedance

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Treatment Temperature



Time to cell death → 15 mins 20 secs 2 secs <1 sec

45°C 50°C 55°C 100°C

- Target temperature ~100°C to avoid charring and loss of heat conduction with a minimum target temperature of 70°C
- Impedance based system target of 200 – 500 Ω

Bhowmick Int J Hypertherm 2004

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Intraoperative Monitoring

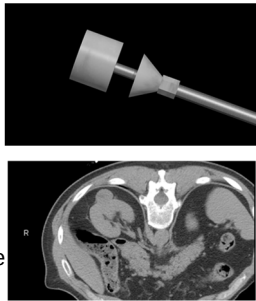
- Limited ability for precise visualization of treatment zone
- Temperature probes around the periphery of tumor for real-time treatment temperature



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RFA: Surgical Technique

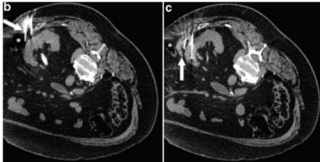
- Performed laparoscopically or percutaneously
- Two 5-8 minute ablation cycles
- Contrast enhanced CT to assess treatment success
 - Repeat treatment, as necessary
 - Tumor size and location impact
 - Heat-sink effect
- Patient are discharged home same day or within 24 hours



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Approach to Challenging Cases

Tumor Proximity to Bowel

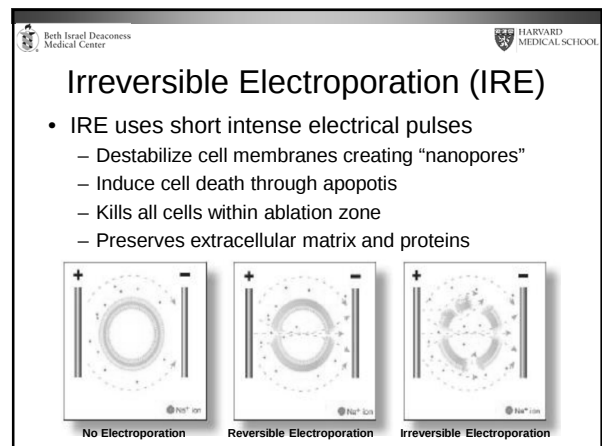
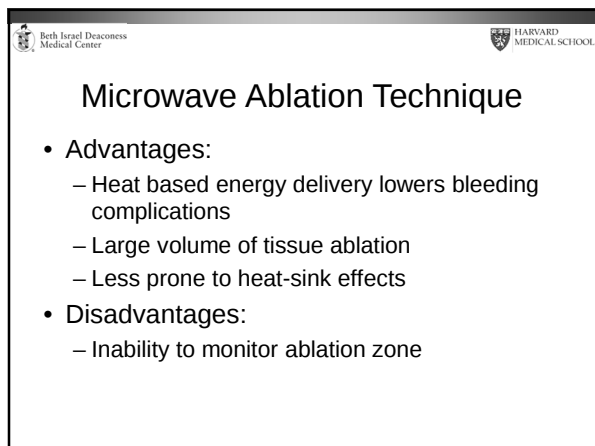
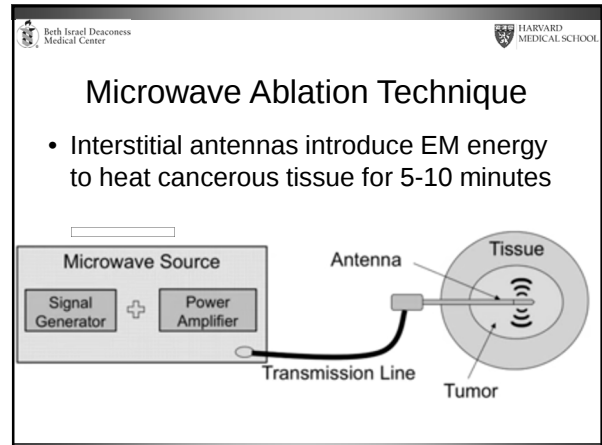
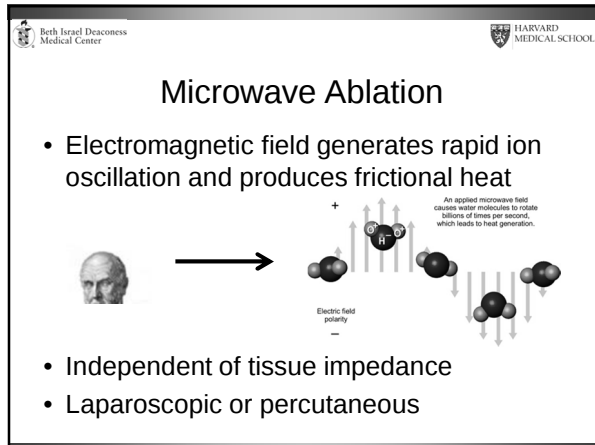
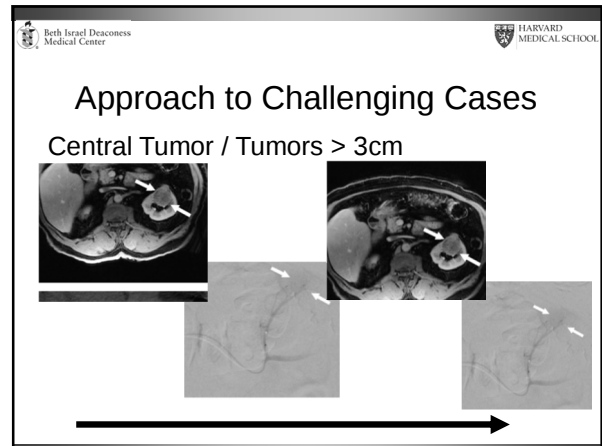
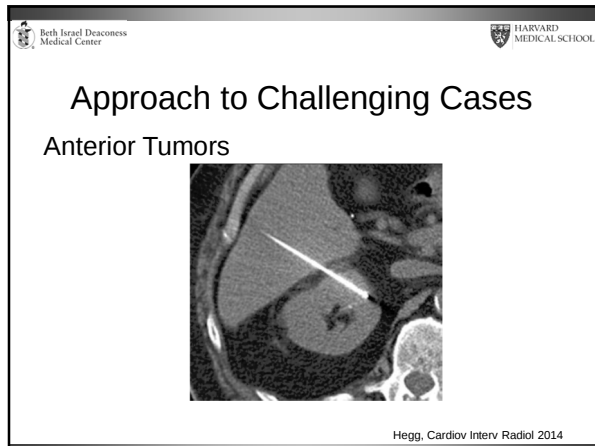


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Approach to Challenging Cases

Tumor Proximity to Nerves

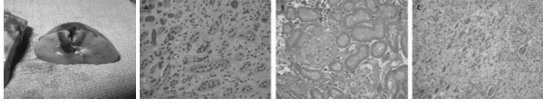




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Irreversible Electroporation

BJUI Irreversible electroporation (IRE): a novel method for renal tissue ablation
 Chad R. Tracy, Wareef Kabbani* and Jeffrey A. Caddeu*
 Department of Urology, University of Texas, Texas A&M Health Science Center, Houston, TX, USA
 Accepted for publication 1 May 2015



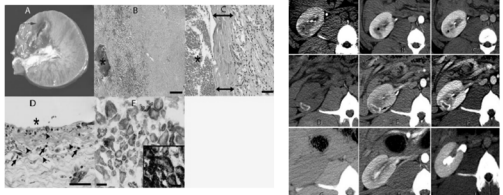
1 Hour 7 Days 14 Days

Necrosis → Chronic Inflammation → Cellular Contraction

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IRE: Preclinical animal studies

- IRE of pig renal pelvis (15 pigs /18 kidneys)
 - Acute phase urothelium 'complete' necrosis & sparing extracellular matrix
 - Later phase cortical necrosis and regeneration of pelvic epithelium
 - 6 pig follow-up: 4/6 complete resolution of IRE zone on CT after 3 weeks

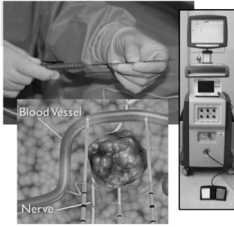


Deodhar Urology 2011

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Irreversible Electroporation: Technique

- General anesthesia + muscle relaxation
 - Contraindications: ventricular arrhythmia
- Needle electrodes
 - 2cm inter-electrode distance
 - 2 to 6 needles to cover
- Approach:
 - Laparoscopic
 - CT or US guided
- Insufficient intermediate- and long-term follow-up



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Outcomes

- Complications
- Renal Function
- Defining Treatment Success
- Long-Term Oncologic Outcomes

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Complications

CA	RFA/MWA
• Perinephric hematoma	• Hematuria
• Genitofemoral nerve injury	• Fank numbness
• Cryoshock	• Perinephric hematoma
• Respiratory failure	• Ileus
• Hematuria	• Urinary retention
• Urinary leak	• Fank bruising
• Hemorrhage	• Urinoma
• Postoperative ileus	• Fank pain
• Ureteropelvic junction obstruction	• Pneumonia
• Pneumonia	• Hemorrhage
	• Neuropathic pain
	• Hydronephrosis
	• Ureteral stenosis
	• Urinary fistula

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Complications

- Typically due to uncontrolled energy distribution outside target zone
- 2017 AUA meta-analysis
 - No difference in major complications between CA (4.9%) and RFA (6.0%)
 - Overall lower risk of complications compared to laparoscopic or open PN

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Complications

- Paresthesia at insertion site (4%)
- Perinephric hematomas (14%)
- Hematuria
- Hemorrhage (11%)
 - Transfusion (5%)
 - Angiography (3%)
 - Less common after RFA (2.4%)

Farrell Am J Roentgenol 2003
Atwell J Vasc Interv Radiol 2012

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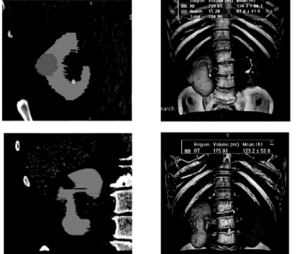
Complications

- Paresthesia at insertion site (4%)
- Perinephric hematomas (14%)
- Hemorrhage (11%)
 - Transfusion (5%)
 - Angiography (3%)
 - Less common after RFA (2.4%)
- Urothelial injury / Urinary leak or stricture (5%)
 - Less common after CA (1-2%)
- Pleural injury / Pneumothorax (1%)
- Bowel injury (1%)

Farrell Am J Roentgenol 2003
Atwell J Vasc Interv Radiol 2012
Zargar Eur Urol 2016

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Renal Function Outcomes



- Matched pair and multivariate analysis showed needle ablative thermal therapies result in less parenchymal loss

Woldu J Endo 2015

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Renal Function Outcomes

	Thermal Ablation	Partial Nephrectomy	p-value
Postop imaging (months)	4.0 ± 2.3	5.2 ± 1.6	<0.005
Change in normal renal parenchyma	-8.1% ± 8.0	-16.5% ± 11.9	<0.005
GFR change	-8.2% ± 13.9	-13.7% ± 14.4	0.004

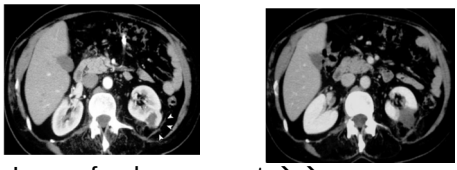
- Ablative techniques can minimize normal parenchyma loss and improve long-term renal function compared to mass excision.

Woldu J Endo 2015

Beth Israel Deaconess Medical Center HARVARD MEDICAL SCHOOL

Outcomes: Defining Treatment Success

- CT or MRI at 6-12 weeks



- Loss of enhancement → success

Matsumoto ED, J Urol 2006

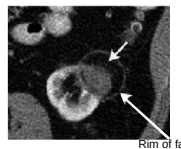
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Assessing Treatment Success

Differences in radiographic appearance:

- Heat-Based Ablation: No change in size

– Halo sign present in ~ 75% cases



Rim of fat surrounding lesion

Schirmag, Vasc and Int Radiology 2009

Assessing Treatment Success

Differences in radiographic appearance:

- Heat-Based Ablation: No change in size
- Cryoablation: ↓ in size by > 50%

Follow-up Time	Cryosize (mm)	Reduction (%)
1 d	44.5 ± 9.4 (45)	—
1 mo	36.3 ± 5.1 (45)	18
6 mo	22.2 ± 6.0 (45)	27
12 mo	17.8 ± 5.5 (45)	43
18 mo	13.1 ± 7.0 (14)	60
2 y	13.1 ± 7.0 (14)	80
3 y	8.9 ± 7.0 (10)	73
4 y	8.1 ± 6.4 (10)	76
5 y	5.1 ± 6.8 (9)	83
6 y	4.0 ± 5.7 (9)	87

Guazzoni, Urology 2010

Follow-up Protocol

- AUA Guidelines
 - CT or MRI with contrast at 3 and 6 months, then annually for 5 years
- Post-ablation biopsy
 - Controversial
 - No enhancement → 17 % still stain H&E positive for viable RCC 6 months post ablation

Oncologic Outcomes

AUTHOR	NO. PATIENTS (NO. TUMORS)	FOLLOW-UP (yrs) (RANGE)	TUMOR SIZE (mm) (RANGE)	TECHNIQUE	% LOCAL RECURRENT FREE SURVIVAL	% METASTATIC RECURRENT	% OVERALL DISEASE-FREE SURVIVAL	% CANCER-SPECIFIC SURVIVAL	% OVERALL SURVIVAL
Pudis et al. 2013	185 (185)	Median 6.43 (0.5-13.4)	Median 3 (1-6)	Perc	5-yr: 95.2	5-yr: 95.4	5-yr: 87.6	5-yr: 98.4	5-yr: 73.3
Tracy et al. 2010	160 (176)	Mean 2.25 (0.15-7.5)	Mean 2.4 (1.0-5.4)	Perc and Lap	5-yr: 90	5-yr: 95	5-yr: 93	5-yr: 95	5-yr: 85
Zigaris et al. 2011	41 (48)	Median 4.67 (0.7-12)	Median 2.6 (0.7-6.2)	Perc	5-yr: 98	5-yr: 93	5-yr: 93	141 (141) of 141	5-yr: 98
Owen et al. 2012	37 (37)	Median 6.5 (0.8-12)	Median 2.1 (0.2-8)	Perc and Lap	5-yr: 91.7	5-yr: 97.2	5-yr: 89	5-yr: 97.2	5-yr: 97.2
Levinson et al. 2008	18 (18)	Mean 4.8 (0.4-6.7)	Mean 3.2 (1-6)	Perc	5-yr: 79.9	5-yr: 100	5-yr: 79.9	5-yr: 100	5-yr: 58.3
McDougal et al. 2005	16 (20)	Mean 5.8 (1.4-11)	Mean 1.9 (0.6-5)	Perc	4-yr: 91	4-yr: 100	—	4-yr: 100	4-yr: 68.7
Arora et al. 2013	222 (256)	Mean 4.8 (1.2-11)	Mean 2.1 (0.6-5)	Perc	5-yr: 96.1	5-yr: 96.1	—	5-yr: 96.1	—
Arora et al. 2010	55 (55)	Median 7.8 (0-11)	Median 2.3 (0.5-5.5)	Lap	87.3	89 MFR	5-yr: 81	5-yr: 85	5-yr: 56
Guazzoni et al. 2010	44	Mean 5.1 (0.5-11)	Median 2.14 (0.5-6)	Lap	93.2	95.5 MFS	—	5-yr: 85	5-yr: 93.2
Tampho et al. 2012	35	Mean 6.3 (SD 3.3)	Mean 2.5 (SD 0.98)	Lap	6-yr: 95.8	6-yr: 100	6-yr: 80	6-yr: 100	6-yr: 76.2

Cryoablation vs Radiofrequency Ablation

No difference seen between CA and RFA:

- 1, 3, and 5-year local-recurrence free survival
- Cancer-specific survival
- Metastatic progression
- Complication rates
- Post-treatment renal function

Atwell Am J Rad 2013
El Dib BJU 2012
Hegarty Urol 2006
Kunkle Cancer 2008

Oncologic Outcomes

Study	Design	Technique	No. of patients	Age (years)	Follow-up (years)	Tumor size (cm)	Recidival disease (%)	Local recurrence (%)	Metastases (%)	MFS (%)	OS (%)	CRS (%)
Pudis et al. (2013)	Retrospective	Perc	185	73 (median)	6.43 (median)	3 (median)	13	0.5	2.2	87.6 (5 years)	98.4 (5 years)	73.3 (5 years)
Guazzoni et al. (2010)	Prospective	Perc	44	68 (median)	5	2.8 (median)	1.5	3	0	97 (5 years)	97.8 (5 years)	100 (5 years)
Tracy et al. (2010)	Retrospective	Lap	160	57 (median)	2.25 (median)	2.4 (median)	0	3.8	0	94.2 (5 years)	95.7 (5 years)	100 (5 years)
Wakai et al. (2013)	Retrospective	Perc	165	67.7 (median)	3.8 (median)	2.9 (median)	4.5	2.5	2	95.8 (5 years)	95.8 (5 years)	97.9 (5 years)
Klein et al. (2013)	Retrospective	Perc	104	67.6 (median)	1.7 (median)	2.3 (median)	8.2	1	nc	nc	nc	nc
Kim et al. (2013)	Retrospective	Perc	124	72.6 (median)	2.3 (median)	2.7 (median)	nc	nc	nc	85 (5 years)	85 (5 years)	100 (5 years)
Kim et al. (2013)	Retrospective	Lap	79	63.8 (median)	4.9 (median)	2.3 (median)	2.3	3.8	0	93.3 (5 years)	73 (5 years)	100 (5 years)
Kim et al. (2013)	Retrospective	Lap	142	63 (median)	4.3 (median)	2.4 (median)	3	3.7	1	91 (5 years)	nc	nc
Elson et al. (2013)	Retrospective	Perc	367	nc	1.8 (median)	2.9	1.3	0.1	nc	nc	87.7 (5 years)	nc
Perlmutter et al. (2013)	Retrospective	Perc	29	64 (median)	3.4 (median)	2.2	38	21	nc	90	97	nc
Kim et al. (2013)	Retrospective	Perc	33	60 (median)	3.4 (median)	2.9	0	6	nc	91	100	nc
Kim et al. (2013)	Retrospective	Perc	267	69.3 (median)	3.3 (median)	2.3 (median)	nc	nc	nc	83.1 (5 years)	77.1 (5 years)	94.4 (5 years)
Chang et al. (2013)	Retrospective	Perc	37	67.2 (median)	1.8 (median)	2.3 (median)	nc	nc	nc	100 (5 years)	97.2 (5 years)	100 (5 years)
Chang et al. (2013)	Retrospective	Perc	37	63.8 (median)	0.5 (median)	2.1 (median)	3.4	8.1	2.7	89.2 (5 years)	97.2 (5 years)	97.2 (5 years)
Kim et al. (2014)	Retrospective	Perc	37	64.8 (median)	0.1 (median)	2.3 (median)	0	8.1	8.1	89.2 (5 years)	100 (5 years)	100 (5 years)
Kim et al. (2014)	Retrospective	Perc	31	71.4 (median)	2.4 (median)	4.8 (median)	12	0	8.2	nc	97 (5 years)	100 (5 years)
Kim et al. (2014)	Retrospective	Perc	222	68.8 (median)	3.2 (median)	1.8 (median)	0.4	3.2	1.8	95.2 (5 years)	nc	nc
Kim et al. (2014)	Retrospective	Perc	163	68.3 (median)	1.8 (median)	2.4 (median)	2.1	2.8	0	95.6 (5 years)	nc	nc

Wagstaff Curr Opin 2015

Oncologic Outcomes

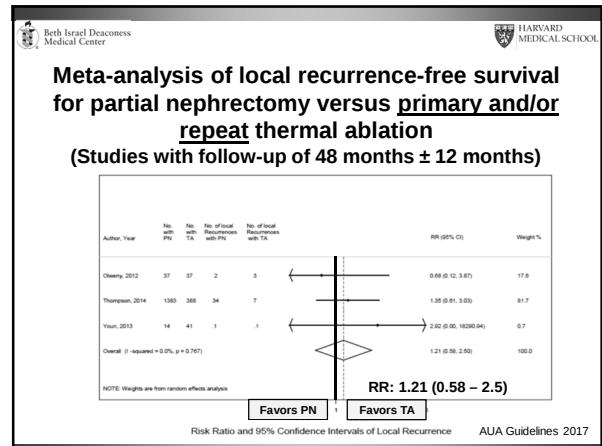
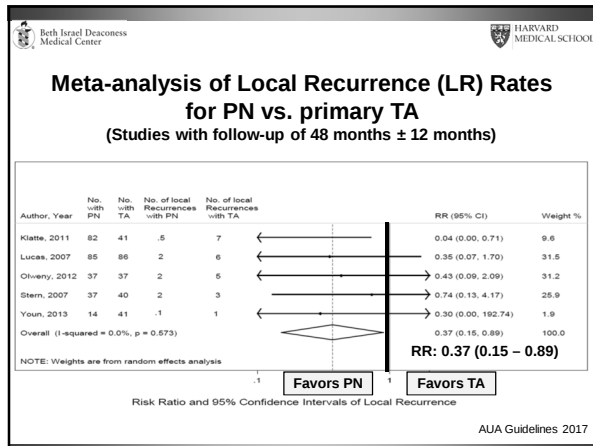
AHRQ Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

Comparative Effectiveness Review
Number 167

Management of Renal Masses and Localized Renal Cancer

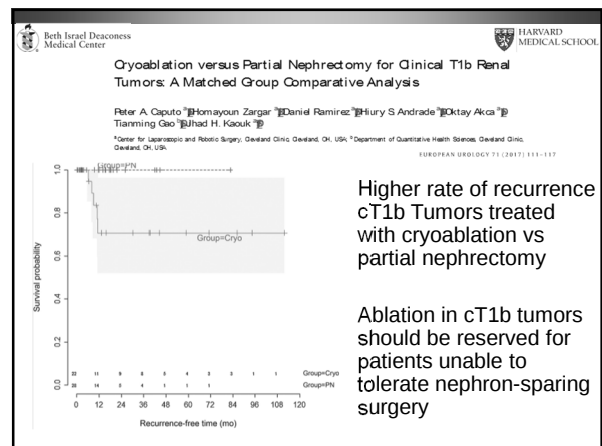
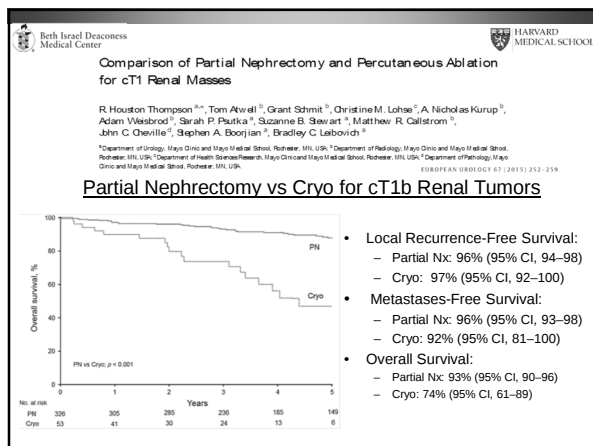
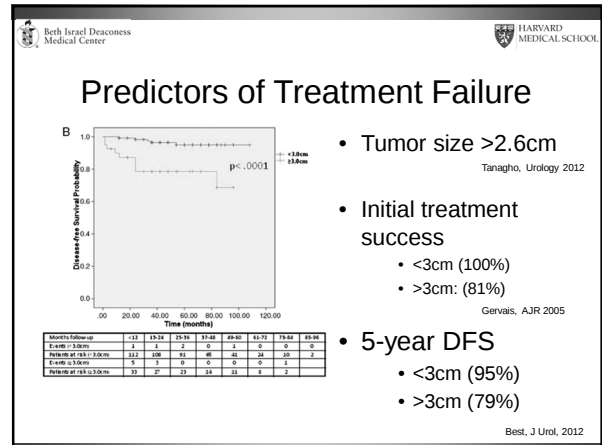
- Comparable metastasis-free survival
 - Partial Nephrectomy: 100% (97 - 100%)
 - Thermal Ablation: 94% (92% - 97%)

Pierorazio AHRQ Comp Effectiveness Review, 2016



Oncologic Outcomes

- Local recurrence free survival in favor of PN over TA
- When you include salvage treatment, then the effect is less obvious
- No information is available on cystic lesions
- So what predicts failure





Conclusions

- Minimally invasive options are expanding
- Partial Nephrectomy remains gold standard for NSS
- Long term oncologic f/u still required
- Ablative therapies may be appropriate in certain patient populations



Acute kidney injury

Melanie P. Hoenig
Associate Professor
Harvard Medical School
Beth Israel Deaconess Medical Center

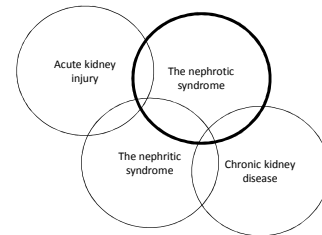
Disclosure

- Editor for KSAP (Kidney Self Assessment Program), a board review and MOC product from American Society of Nephrology

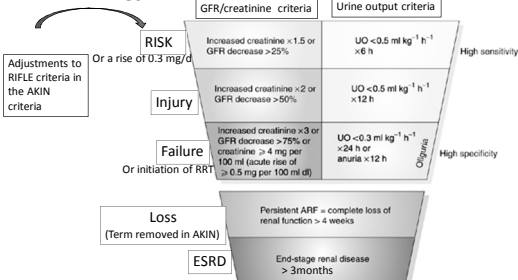
Acute kidney injury

- Review of terminology
- Categories of acute kidney injury:
 - Prerenal azotemia
 - Intrinsic renal disease
 - "post" renal
- Complications of AKI
- Management

Terminology



Terminology: AKI vs ARF



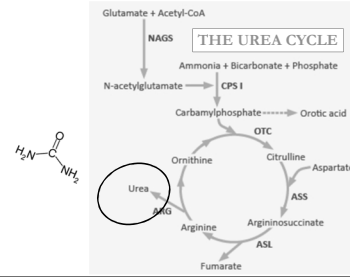
Laboratory testing for assessment of kidney function

- Urine output
- BUN
- Creatinine
- Urinalysis
- Urine protein

Normal urine output

- Normal urine output $\approx$ 800-2liters/day
- Oliguria is <500 ml/day or < 20 ml/hour (or 0.5 ml/kg/h)
- Anuria is < 50 ml/day
- Polyuria is $> 3L$

Urea is relatively nontoxic substance made in the liver to dispose of NH_4^+ generated from protein metabolism



- The kidney filters and reabsorbs
- Increases with high protein meal
- Increases with volume depletion (when more is reabsorbed).
- No formulas to assess kidney function based on urea.

<http://newenglandconsortium.org>

Creatinine

- generated from normal muscle metabolism.
- An average individual makes approximately 1 gram over course of a day.
- Those with more muscle mass will have slightly higher serum creatinine values and those with less will have lower values.



Wroblewski AP et al. Physician and Sports Medicine 39(3) 2011

70-year-old triathlete



Wroblewski AP et al. Physician and Sports Medicine 39(3) 2011

Acute kidney injury

Creat $\uparrow$ 0.3
or $>50\%$

Prerenal
azotemia

Intrinsic
Renal

Post
renal

Acute kidney injury

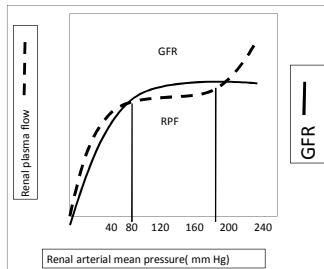
Creat $\uparrow$ 0.3
or $>50\%$

Prerenal
azotemia

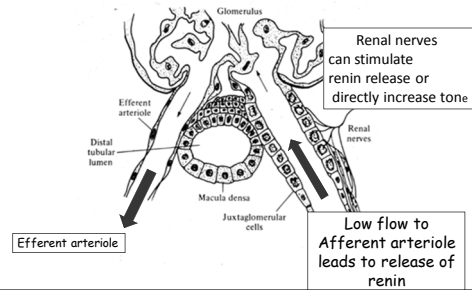
Intrinsic
Renal

Post
renal

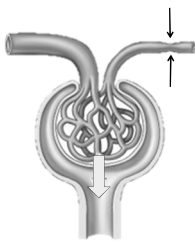
The kidney must maintain filtration over a wide range of perfusion pressures



Glomerular filtration is regulated by:
① flow to the arteriole



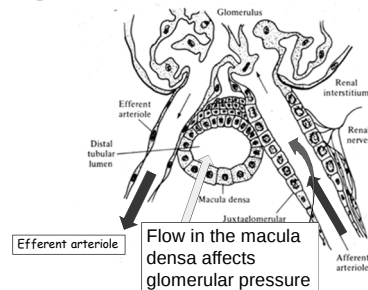
ANGIOTENSIN II



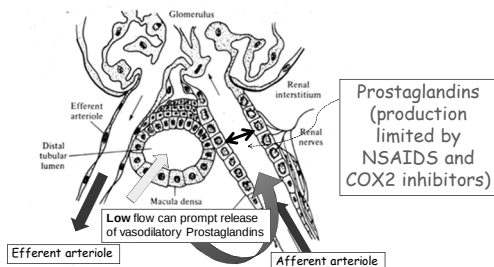
1. **Potent** systemic vasoconstrictor
2. Retention of sodium and water throughout the nephron (esp in proximal tubule)
3. Regulation of glomerular filtration by vasoconstriction of EA>AA
4. Stimulates release of aldosterone

(affect blocked by ACE inhibitors and ARB)

Glomerular filtration is also affected by:
② tubular flow (tubuloglomerular feedback)



Glomerular filtration and tubuloglomerular feedback



Characteristics of Prerenal azotemia

1. Clinical history of volume depletion from losses or relative hypotension

2. Elevated BUN to creatinine ratio

Volume Depletion
GI Bleeding
Steroids-high catabolic rate
High Protein intake
Low muscle mass (creatinine rises little)

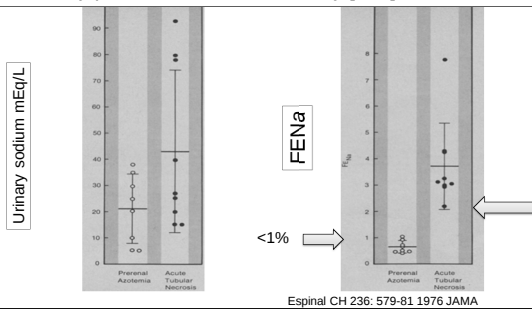
$\frac{\text{BUN}}{\text{Creatinine}}$

3. Low urinary sodium and/or FENa

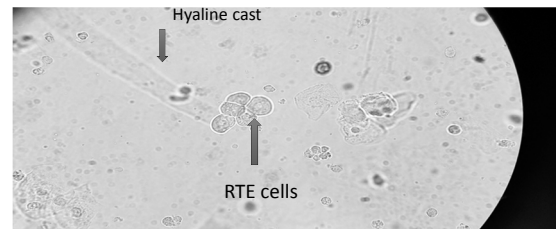


$$\text{FENa} = \frac{U_{\text{Na}} * P_{\text{Cr}}}{P_{\text{Na}} * U_{\text{Cr}}} \times 100\%$$

The FENa may perform better than urinary $[\text{Na}^+]$



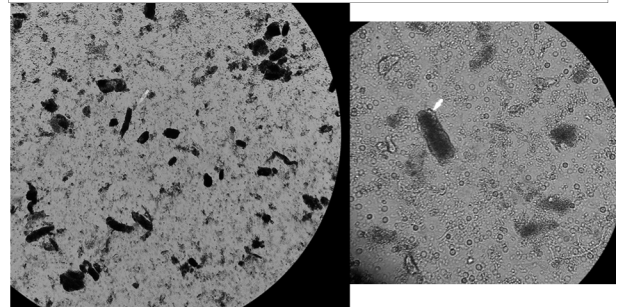
4. Urine sediment should be bland or feature hyaline casts.

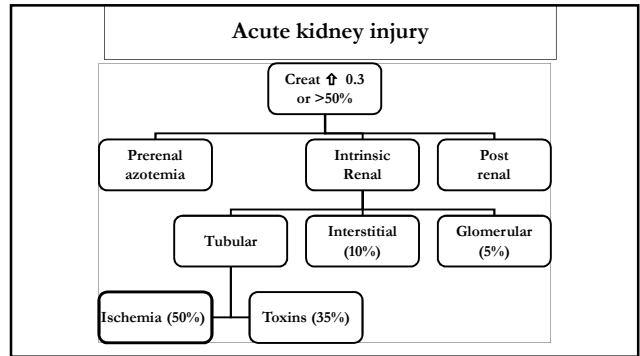
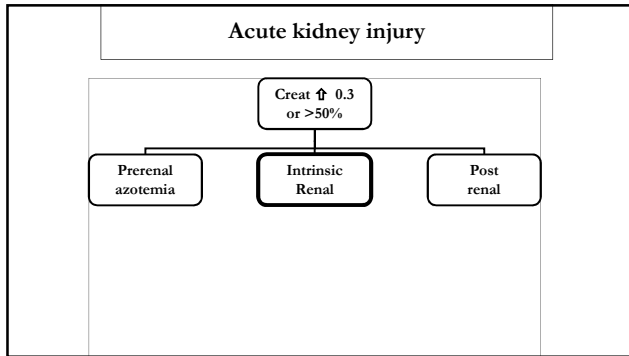


Prerenal azotemia

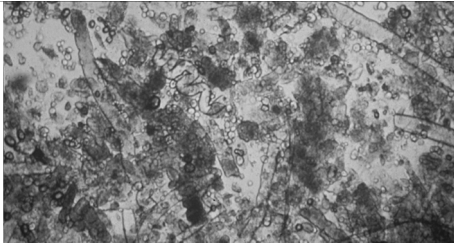
- High BUN to creatinine ratio
- Bland urinary sediment (or hyaline casts)
- Low urinary sodium
- Low FENa
- High urine osmolality (or specific gravity)

Yet if volume depletion continues, tubular injury can ensue.

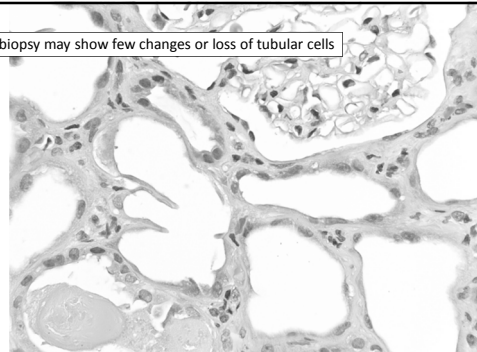




First, a focus on acute tubular necrosis (ATN)



Renal biopsy may show few changes or loss of tubular cells



Differentiating between 2 most common types of AKI

	Prerenal azotemia	ATN
urine sediment	Benign	Casts, tubular cells
Urine osmolarity	> 500 mOsm/L	< 350 mOsm/L
Urine [Na ⁺]	< 10 mEq/L	> 20 mEq/L
FENa = $\frac{U_{Na}/P_{Na}}{U_{creat}/P_{creat}}$	< 1 %	> 2 %

Tubular damage can also occur from toxic injury:

- Myoglobin
- Aminoglycosides
- Iodinated contrast

Rhabdomyolysis with renal failure

Case reports with

1. exaggerated lithotomy position
2. Laparoscopic donor nephrectomy or laparoscopic nephrectomy
3. Plus--Trauma victims who are also receiving urologic care

Presentation:

severe muscle pain
tea colored urine
Elevated CPK

Treatment:

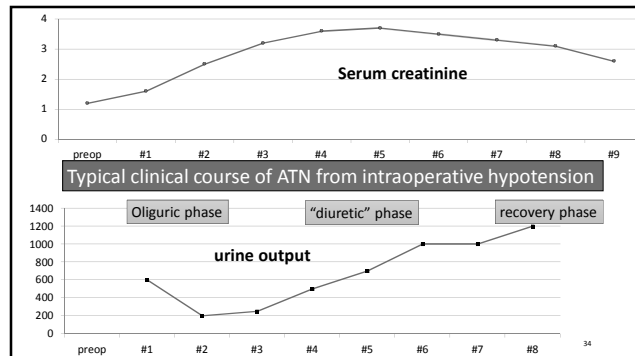
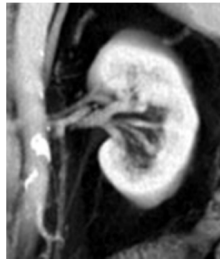
Forced alkaline diuresis (or simply fluid resuscitation)

Contrast Induced Nephropathy (CIN)

- Considerable decline in incidence with preventative measures
- Characterized by an abrupt decline in kidney function 24-48 hours after receiving intravenous iodinated contrast
- Results from combination of direct tubular toxicity and renal ischemia (secondary to renal vasoconstriction)
- Risk factors: diabetes mellitus, baseline renal impairment and volume depletion

Precautions for iodinated contrast

- Avoid studies with volume depletion
- Hold ACE I, ARB, diuretics and NSAIDS prior to procedure if possible
- IVF hydration
several protocols (ie Pre: 3cc/kg/hr X 1 hour;
Post: 1cc/hr X 6 hrs)
Consider N-Acetyl cysteine
- Non-ionic agents or "low" osmolar agents in smallest possible dose

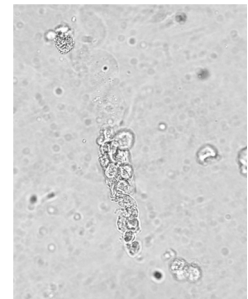


Acute interstitial nephritis

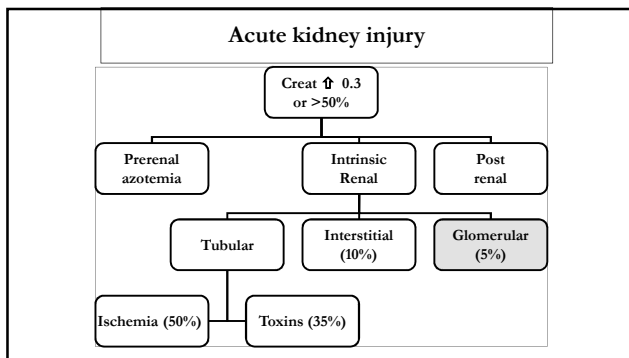
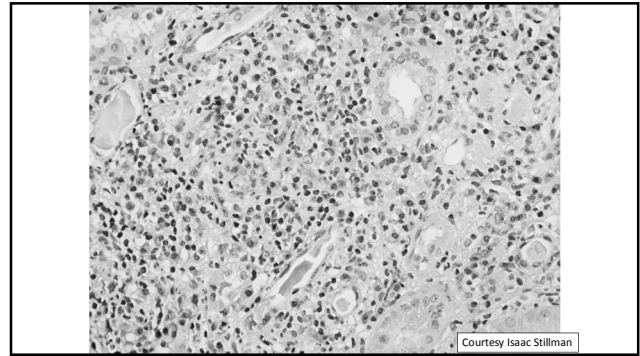
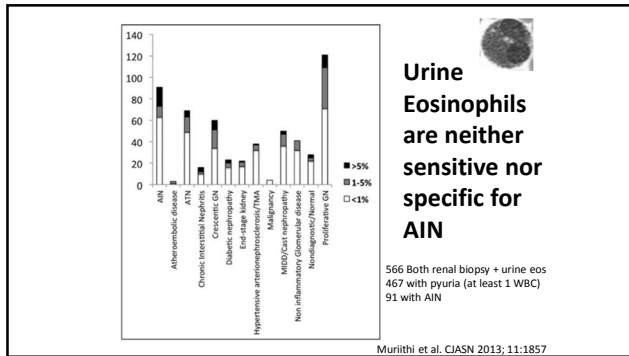
- Classic triad (for acute interstitial nephritis):
 - Rash 15%
 - Fever 27%
 - Eosinophilia 23%
 - All three 10%
- Decline in renal function
- Proteinuria usually mild

Baker RJ and Pusey CD NDT 2004 ; 19(1): 8-11
Summary of 3 small series= 128 patients

- Dipstick
 - Mild proteinuria
 - Isothenuria
 - $\pm$ glycosuria
- Urine sediment
 - Classically: WBC and WBC casts
 - Often bland



M Hoenig's iPhone



AKI is very uncommon in glomerular disease characterized by nephrotic syndrome

- Minimal change disease with heavy proteinuria
- Collapsing FSGS

AKI does occur with Glomerulonephritis

- Acute nephritic syndrome-days to weeks
- Rapidly Progressive Glomerulonephritis-weeks to months

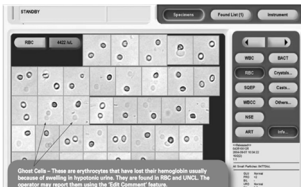
<https://library.med.utah.edu/WebPath/TUTORIAL/URINE/URINE.html>

AKI does occur with Glomerulonephritis

- Hallmark is an active urinary sediment: typically with acanthocytes, cellular casts
- Proteinuria
- Altered renal function
- Hypertension
- Potentially edema
- Multiple causes- symptoms depend on whether it is renal limited or systemic disorder and pace of clinical course

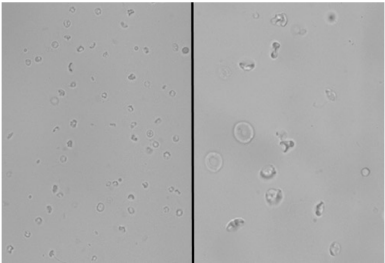
<https://library.med.utah.edu/WebPath/TUTORIAL/URINE/URINE.html>

Urinalysis performed by the laboratory is excellent for cell count on fresh specimen but may be less useful for cell morphology than microscopy.

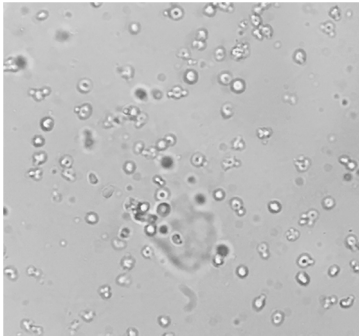


<http://www.irisdiagnostics.com/clinical-info/urinalysis-basics>

RBC in urine for any cause may have abnormal shapes

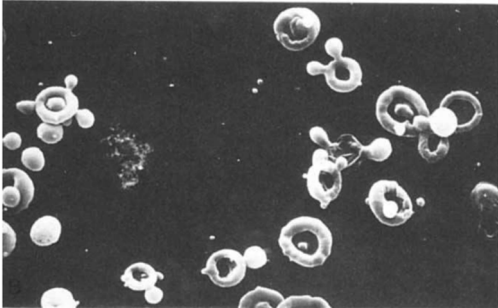


Cohen R and Brown R NEJM 2003

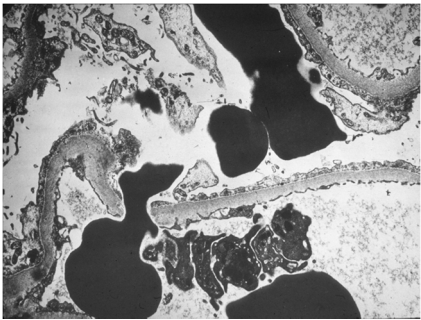


Glomerular bleeding may have unique features

Melanie Hoenig's iPhone

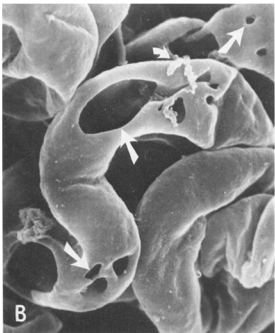


Kohler R Wandel E and Brunch B. Kidney Intl 1991;40:115-120

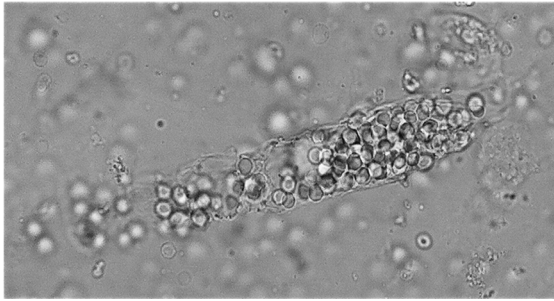


Courtesy of Helmut Rennke

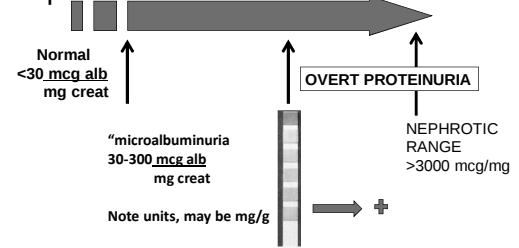
Scanning electron microscopy of an acellular glomerulus in a patient with glomerulonephritis to highlight the rupture of the GBM



Bosnib SM Am J Pathol 1985



Patients with glomerulonephritis also have proteinuria

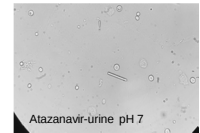
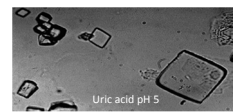


“post renal”
AKI

- Tubular obstruction by crystals
- Extrinsic obstruction
- Intraluminal obstruction

“post renal”
AKI

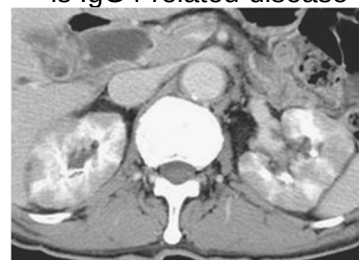
- Tubular obstruction by crystals
 - Oxalate nephropathy (hyperoxaluria)
 - Uric acid (tumor lysis syndrome)
 - Exogenous agents such as protease inhibitors (indinavir, raltegravir) and acyclovir



Extrinsic renal obstruction

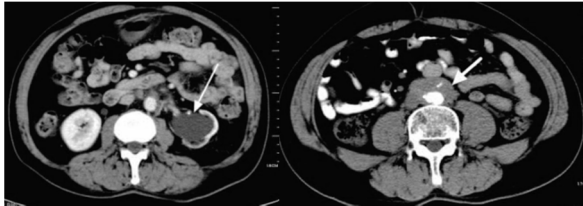
- Malignancy-common
- Retroperitoneal fibrosis-rare

A rare cause of extrinsic obstruction is IgG4-related disease

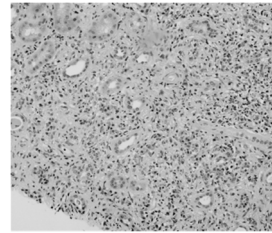


Saeki Kidney Int 2013

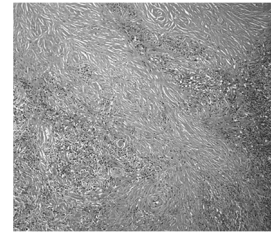
IgG4-related disease can cause retroperitoneal fibrosis



Lei W et al. Medicine 2016



Dense lymphocytic infiltrate of the kidney



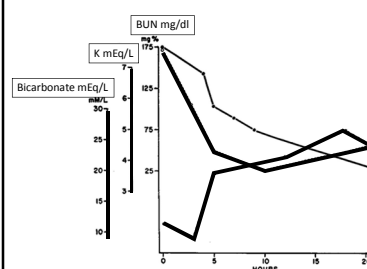
Storiform fibrosis

Images courtesy of Vanessa Bijol MD

Management issues following relief of obstruction

- Acute
 - Electrolytes
 - volume
- Chronic
 - Long term urologic management
 - Potential incomplete recovery of renal function

Rapid Improvement in Serial Serum Chemical Findings during Post obstructive diuresis Osmotic Diuresis.

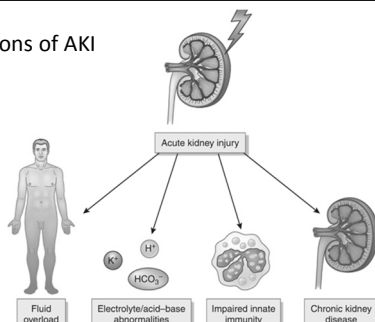


Maier JF et al. N Engl J Med 1963;268:1099-1104.

Following relief of obstruction, significant urine output may ensue:

1. Excretion of retained sodium and water
2. Excretion of accumulated urea may lead to an osmotic diuresis
3. If polyuria persists after 24 hours or after euvolemia and/or if the patient cannot take fluids orally, IV fluid may be required

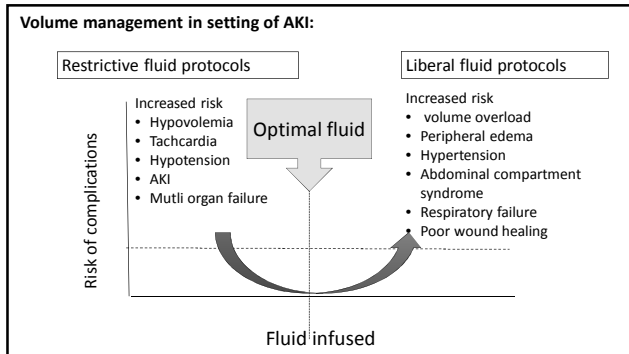
Complications of AKI



Singbarti K Kellum JA Kidney Int 2012 81: 819-825

Management of Patients with AKI

- Treat underlying cause when possible
- Discontinue all non-essential potential nephrotoxins
- **Modify Drug dosages (may need to assume GFR=0)**
- Review diet and IV fluid to avoid hyperkalemia, hyponatremia and metabolic acidosis
- Diuretics do not “convert” oliguric to non-oliguric but patients who respond may have better prognosis or easier management
- Kidney replacement therapy if necessary



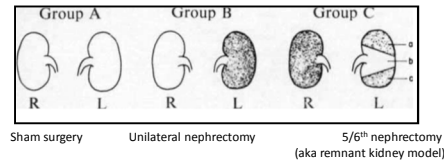
Indications for dialysis in patients with AKI

- Classic Indications
 - Hyperkalemia
 - Severe Metabolic Acidosis
 - Diuretic resistant volume overload
 - Uremic signs or symptoms
 - Certain Drug intoxications
- Additional potential indications
 - Refractory volume overload and desire to limit further volume excess

Prognosis for AKI varies by cause, comorbid conditions and prior renal function

- Prerenal azotemia is benign
- ATN in the ICU is more severe
 - 50 % mortality
 - 25% complete recovery
 - 20% incomplete
 - 5% no recovery

Best treatment of AKI is prevention



(Experimental models often use the 5/6th nephrectomy model to induce AKI)

Kaufman KI 1974

Comprehensive Review of Urology

Chronic Kidney Disorders

David Steele MD
Renal Unit
Massachusetts General Hospital
Boston MA.

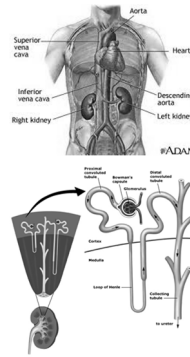
Disclosures

- Reports no relationships with a commercial interest

Aims

- Gather a sense of the demographics and natural history of Chronic Kidney Disease (CKD)
- Understand the impact of CKD on the patient and it's associated co-morbidities
- Review ESRD management options including medical management

Nephrology Factoids



- Kidneys get ~ 20% of cardiac output
- Generate ultrafiltrate of 180L a day
- Produce 1-1.5L urine output
- Excrete ~ 600-800 mosm
- Regulates
 - Volume (Na Metabolism)
 - Tonicity (Water Metabolism)
 - Potassium metabolism
 - Acid/Base balance
 - Excretion of Nitrogenous wastes
 - Anemia (Erythropoetin)
 - Bone metabolism (1 alpha Hydroxylase)
 - Blood pressure (Renin)

Google: "Free Images"

Question

A 55 year-old man, with a history of type 2 diabetes (15 years), hypertension (3 years) dyslipidemia (5 years) and cardiovascular disease (myocardial infarction 3 years ago). He was recently diagnosed with CKD. His most recent labs reveal an eGFR of 45 ml/min/1.73m² and an ACR of 38 mg/g.

Which of the following should be avoided?

- A. ACE and ARB in combination
- B. Daily low-dose aspirin
- C. NSAIDs
- D. Statins
- E. A and C

www.kidney.org/CKDinform

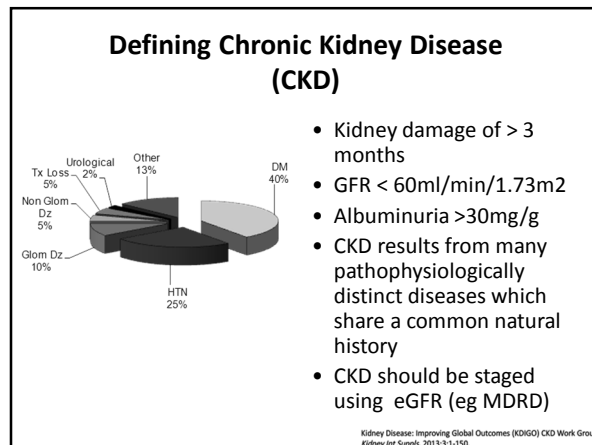
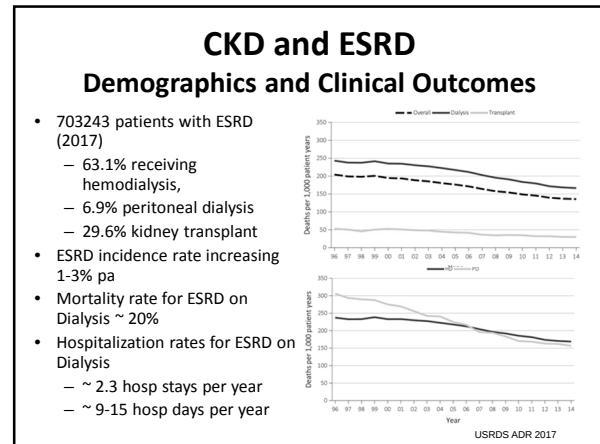
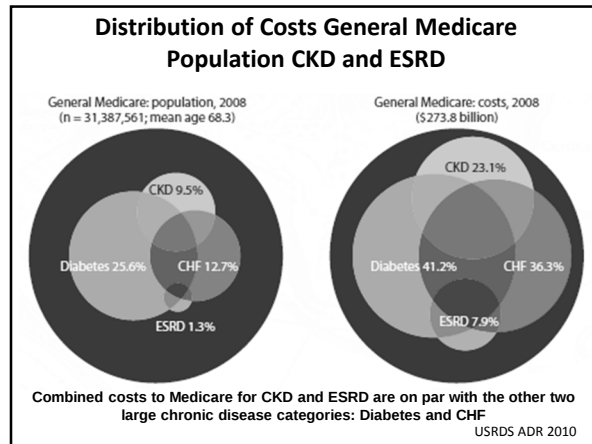
Answer

A 55 year-old Caucasian-American man, with a history of type 2 diabetes (15 years), hypertension (3 years) dyslipidemia (5 years) and cardiovascular disease (myocardial infarction 3 years ago). He was recently diagnosed with CKD. His most recent labs reveal an eGFR of 45 ml/min/1.73m² and an ACR of 38 mg/g.

Which of the following should be avoided?

- A. ACE and ARB in combination
- B. Daily low-dose aspirin
- C. NSAIDs
- D. Statins
- E. A and C

www.kidney.org/CKDinform



Question

69 y.o. male with CAD (four prior MIs), Heart Failure with Reduced Ejection Fraction (HFrEF) (EF=24%), severe Mitral Regurgitation, Paroxysmal Atrial Fib, Ventricular Tachycardia s/p ICD, Hypertension, Hyperlipidemia, CKD (baseline Cr 1.4), metastatic prostate cancer (on leuprolide), admitted for HFrEF exacerbation with course complicated by oliguric renal failure and concern for worsening cardiogenic shock, transferred to CCU for tailored therapy. Renal Artery Duplex Ultrasound negative for Renal Artery Stenosis. Renal function remains impaired despite optimizing CHF regimen. Work up of AKI should include:

- Repeat Renal Ultrasound
- Renal Biopsy
- Renal Nuclear Medicine Scan
- Upper extremity venous mapping for AV Fistula
- No additional work up needed

Answer

69 y.o. male with CAD (four prior MIs), Heart Failure with Reduced Ejection Fraction (HFrEF) (EF=24%), severe Mitral Regurgitation, Paroxysmal Atrial Fib, Ventricular Tachycardia s/p ICD, Hypertension, Hyperlipidemia, CKD (baseline Cr 1.4), metastatic prostate cancer (on leuprolide), admitted for HFrEF exacerbation with course complicated by oliguric renal failure and concern for worsening cardiogenic shock, transferred to CCU for tailored therapy. Renal Artery Duplex Ultrasound negative for Renal Artery Stenosis. Renal function remains impaired despite optimizing CHF regimen. Work up of AKI should include:

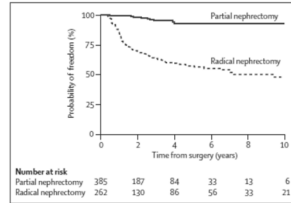
- Repeat Renal Ultrasound
- Renal Biopsy
- Renal Nuclear Medicine Scan
- Upper extremity venous mapping for AV Fistula
- No additional work up needed

Obstructive Uropathy

- Urinary tract obstruction should always be ruled out in patients with CKD and AKI on CKD
- In the absence of prostate disease renal perfusion is a much more likely cause of AKI/CKD
- Obstructive Uropathy is often asymptomatic
- If obstruction is present as the cause the urine sediment is often non diagnostic
- Recording bladder residual volume and dedicated renal ultrasound may be diagnostic

Chronic kidney disease after nephrectomy in patients with renal cortical tumours

- Retrospective cohort study of 662 patients
- 3-year probability of freedom from new onset of GFR lower than 60 mL/min
 - 80% (95% CI 73–85) after partial nephrectomy
 - 35% (28–43; $p < 0.0001$) after radical nephrectomy;
- 3-year probability of freedom from new onset of GFRs lower than 45 mL/min
 - 95% (91–98) after partial nephrectomy
 - 64% (56–70; $p < 0.0001$) after radical nephrectomy,



Huang et al *Lancet Oncol* 2006; 7: 735–40

Kidney Stones and Kidney Function Loss

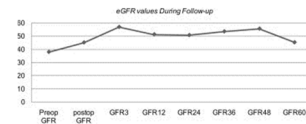
1 954 836 patients with outpatient serum creatinine measurements and one or more kidney stones during follow up.

Subgroup	Unadjusted ESRD rate		Hazard ratio (95% CI)	Hazard ratio (95% CI)
	Kidney stones	No kidney stones		
First kidney stone episode during follow-up v no kidney stones				
Overall	2.48	0.52		2.16 (1.79 to 2.62)
≥50 years old	4.68	1.43		2.01 (1.61 to 2.49)
<50 years old	1.00	0.23		2.81 (1.96 to 4.03)
Men	2.65	0.64		1.87 (1.49 to 2.34)
Women	2.16	0.40		3.36 (2.42 to 4.66)
Men				
≥50 years old	4.44	1.85		1.85 (1.46 to 2.34)
<50 years old	1.13	0.29		2.43 (1.60 to 3.70)
Women				
≥50 years old	5.44	1.06		2.72 (1.87 to 3.96)
<50 years old	0.81	0.17		3.58 (2.38 to 5.38)
No of kidney stone episodes during follow-up v no kidney stones				
First kidney stone episode	2.36	–		2.11 (1.69 to 2.63)
Second kidney stone episode	2.82	–		2.31 (1.66 to 3.21)

BMJ 2012;345:e5287 doi: 10.1136/bmj.e5287 (Published 30 August 2012)

Long-term Outcomes of Percutaneous Nephrolithotomy in Patients With Chronic Kidney Disease

- Retrospective analysis of 69 PNL procedures in 67 patients
- PNL in patients with chronic kidney disease is safe and results in renal function preservation for a 5-year period.
- Diabetes mellitus and urinary infection were independent predictive of renal function impairment.



Mermet et al *Urology* 79 (5) May 2012

The Acute and Long-Term Adverse Effects of Shock Wave Lithotripsy

James A. McAteer, Ph.D. and Andrew P. Evan, Ph.D.
Department of Anatomy and Cell Biology, Indiana University School of Medicine

- Intraparenchymal and subcapsular and hematomas
- Rupture of renal pelvis
- Proliferative glomerulopathy
- Anti-glomerular basement membrane disease
- Permanent loss of nephrons
- Diffuse fibrosis
- Acellular scarring from cortex to inner medulla
- Complete papillary necrosis
- Irreversible acute renal failure

Semin Nephrol. 2008 March ; 28(2): 200–213.

Chronic kidney disease in urolithiasis patients following successful extracorporeal shockwave lithotripsy

SATOSHI MAEDA¹, TOSHIHIDE NAGANUMA¹, YOSHIKI TAKEMOTO¹,
TETSUO SHOJI², MIKIO OKAMURA³ and TATSUYA NAKATANI¹

Compared 114 patients following successful ESWL and the 96 healthy control subjects
There was an increased prevalence of CKD among patients following ESWL
[40 patients (35.1%) vs. 9 healthy controls (9.4%), $P < 0.0001$].

Variable	Unit increase	Unadjusted		Adjusted ^a	
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1 year	1.067 (1.028–1.107)	0.0006	–	–
Gender (males)		2.884 (1.170–7.107)	0.0214	–	–
Hypertension		6.312 (1.253–6.211)	0.0424	2.011 (0.840–4.811)	0.1165
Diabetes mellitus		1.024 (0.432–2.428)	0.9568	0.711 (0.276–1.828)	0.4787
Dyslipidemia		0.694 (0.292–1.650)	0.2910	0.854 (0.324–2.249)	0.7488
Cardiovascular disease		1.806 (0.637–5.120)	0.2665	1.075 (0.334–3.462)	0.9032
Body mass index	1 kg/m ²	1.107 (1.005–1.220)	0.0399	1.193 (1.058–1.345)	0.0039
Stone position (nephritic stone)		2.443 (1.093–5.461)	0.0295	2.612 (1.075–6.344)	0.0340
ESWL sessions (multiple)		1.105 (0.512–2.387)	0.7989	0.978 (0.419–2.285)	0.9590
Stone size (≥ 10mm)		0.696 (0.290–1.671)	0.4173	0.807 (0.310–2.100)	0.6593

MOLECULAR MEDICINE REPORTS 5: 3–6, 2012

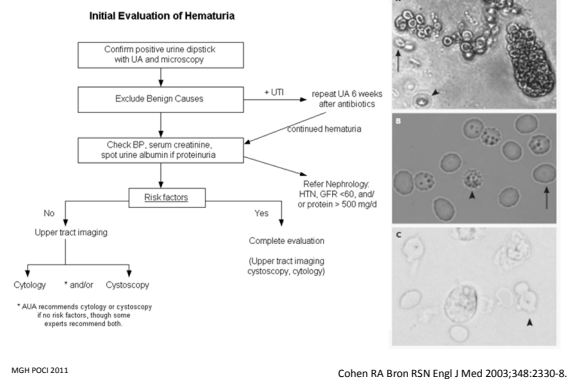
Steps to CKD Patient Care

- Does the patient have CKD?
 - Assess GFR, albuminuria.
- Determine etiology.
- Assess for evidence of progression.
- Assess for associated complications.
- Patient education.
- Assess life expectancy and patient wishes for dialysis/transplantation.

Clinical Evaluation of Patients with CKD

- Blood pressure
- HbA1c
- Serum creatinine
 - Use a GFR estimating equation or clearance measurement; don't rely on serum creatinine concentration alone.
 - Be attentive to changes in creatinine over time—even in "normal" range.
- Urinalysis
 - Urine sediment
- Albuminuria/Proteinuria
 - Spot urine for protein-to-creatinine or albumin-to-creatinine ratio.
- Electrolytes, blood glucose, CBC
- Depending on stage:
 - albumin, phosphate, calcium, iPTH
- Renal imaging
- Depending on age and H&P
 - Light chain assay, serum or urine protein electrophoresis (SPEP, UPEP)
 - HIV, HCV, HBV tests
 - Complements, other serological testing - limited role unless specific reason

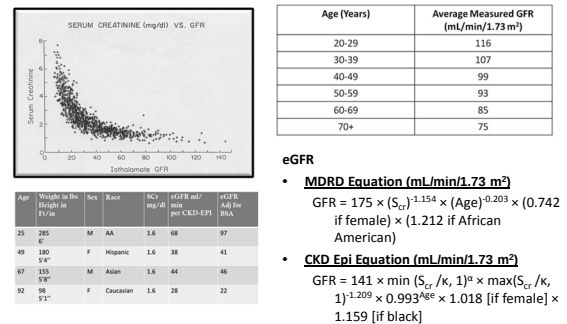
Markers of Renal Disease. Microscopic Hematuria



Markers of Renal Disease: Proteinuria

- 24-hour urine not necessary
- "Spot" urine Protein (or Albumin) to Creatinine ratio recommended
- Example
 - Urine Protein 155 mg/dl
 - Urine Cr 100 mg/dl
- Ratio = 155 mg/dl / 100 mg/dl = 1550 mg/g creatinine
- Microalbuminuria**
 - 30-300mg per 24 hrs
 - Not detectable by dipstick
 - Marker of incipient renal disease
- Proteinuria**
 - 300mg to 3.5grams per 24 hrs
 - Marker of overt renal disease
 - Glomerular injury (usually Albumin)
 - Tubulointerstitial (non Albumin)
- Nephrotic Range Proteinuria**
 - > 3.5 grams
 - Associated with Nephrotic Syndrome
 - Hypoalbuminemia
 - Edema
 - Hyperlipidemia

Markers of Renal Disease: Serum Creatinine



Evaluating CKD

Assign Albuminuria Category

Albuminuria Categories in CKD		
Category	ACR (mg/g)	Terms
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased*
A3	>300	Severely increased**

*Relative to young adult level. ACR 30-300 mg/g for >3 months indicates CKD.
 **Including nephrotic syndrome (albumin excretion ACR >2220 mg/g).

Assign GFR Category

GFR Categories in CKD		
Category	GFR	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mild to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

*Relative to young adult level
 **Relative to evidence of kidney damage, neither GFR category G3 nor G2 fulfill the criteria for CKD. Refer to a nephrologist and prepare for kidney replacement therapy when GFR <30 mL/min/1.73m².

Question

All of the following adult patients should be referred for nephrology consultation, EXCEPT?

- Initial visit: eGFR 26 & 3 months later: eGFR 28 (mL/min/1.73m²)
- Initial visit: eGFR 55, & 3 months later: eGFR 43 confirmed with repeat eGFR 45 (mL/min/1.73m²)
- Initial visit: ACR 450 & 3 months later: ACR 355 (mg/g) on both dates the eGFR >60 mL/min/1.73m²
- Initial visit: eGFR >60 & 3 months later: eGFR >60 (mL/min/1.73m²) with personal history of Autosomal Dominant Polycystic Kidney Disease
- Initial visit: eGFR 42 & 3 months later: eGFR 44 (mL/min/1.73m²) on both dates the ACR <30 mg/g

www.kidney.org/CKDinform

Answer

All of the following adult patients should be referred for nephrology consultation, EXCEPT?

- Initial visit: eGFR 26 & 3 months later: eGFR 28 (mL/min/1.73m²)
- Initial visit: eGFR 55, & 3 months later: eGFR 43 confirmed with repeat eGFR 45 (mL/min/1.73m²)
- Initial visit: ACR 450 & 3 months later: ACR 355 (mg/g) on both dates the eGFR >60 mL/min/1.73m²
- Initial visit: eGFR >60 & 3 months later: eGFR >60 (mL/min/1.73m²) with personal history of Autosomal Dominant Polycystic Kidney Disease
- Initial visit: eGFR 42 & 3 months later: eGFR 44 (mL/min/1.73m²) on both dates the ACR <30 mg/g

www.kidney.org/CKDinform

Classification of CKD Based on GFR and Albuminuria Categories: "Heat Map"

CKD is classified based on:

- Cause (C)
- GFR (G)
- Albuminuria (A)

		Albuminuria categories Description and range		
		A1	A2	A3
		Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-299 mg/g 3-29 mg/mmol	Severely increased ≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m ²) Description and range	G1 Normal or high ≥90	1 if CKD	Monitor 1	Refer* 2
	G2 Mildly decreased 60-89	1 if CKD	Monitor 1	Refer* 2
	G3a Mildly to moderately decreased 45-59	Monitor 1	Monitor 2	Refer 3
	G3b Moderately to severely decreased 30-44	Monitor 2	Monitor 3	Refer 3
	G4 Severely decreased 15-29	Refer* 3	Refer 3	Refer 4+
G5 Kidney failure ≤15	Refer 4+	Refer 4+	Refer 4+	

Colors: Represents the risk for progression, morbidity and mortality by color from best to worst. Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

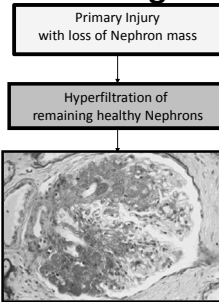
Numbers: Represent a recommendation for the number of times per year the patient should be monitored.

Refer: Indicates that nephrology referral and services are recommended.

*Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referral.

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppl. 2013;3:1-150.

Progression of CKD - Angiotensin II effects

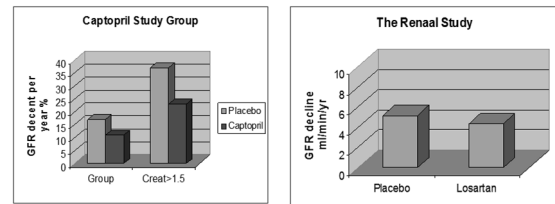


Secondary Focal Segmental Glomerulosclerosis

- Angiotensin II
 - Hemodynamic effects
 - Single nephron increased GFR
 - Increased intraglomerular pressure
 - Non Hemodynamic effects
 - Inflammation and oxidative stress
 - Cellular hypertrophy and proliferation

Decline in GFR: ACEI and ARB use in Type 1 and Type 2 Diabetics

Lewis et al NEJM 329(20), 1993
Brenner et al NEJM 345(12), 2001



Reduction in risk of doubling serum creatinine

- Captopril Study (Lewis) - 48%
- Renal Study (Brenner) - 25%

ACEI/ARB's in CKD

- ACEI or ARB are indicated for diabetic patients with uAlb/Creat ratio>0.03 (microalbuminuria)
 - ACEI or ARB are indicated for CKD patients with uAlb/Creat ratio>0.5 (overt proteinuria)
1. Tolerate a small (15-20%) rise in serum creatinine
 2. Attempt to manage Hyperkalemia without withdrawal of ACEI/ARB:
 - Dietary K restriction
 - Gastrointestinal potassium binders prn
 - Loop diuretics; Fludrocortisone
 3. Use ARB in patients intolerant to ACEI (cough)

Question

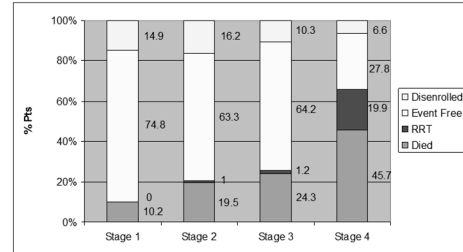
- The Tromsø study looked at the natural history of CKD in a population of 58000 patients in Scandinavia. 3047 patients were found to have a GFR between 30 and 60 ml/min. Patients were followed for 10 years and the rate of progression to ESRD was:
 - A. 4%
 - B. 10%
 - C. 12%
 - D. 25%

Answer

- The Tromsø study looked at the natural history of CKD in a population of 58000 patients in Scandinavia. 3047 patients were found to have a GFR between 30 and 60 ml/min. Patients were followed for 10 years and the rate of progression to ESRD was:
- 4%
 - 10%
 - 12%
 - 25%

Longitudinal Follow-up and Outcomes Among a Population With Chronic Kidney Disease in a Large Managed Care Organization

27998 patients identified with GFR < 90ml/min and followed for 5 years



Arch Intern Med. 2004;164:659-663

Strategies for Caring with Patients with CKD 4

- Delay Progression**
 - ACE Inhibition
 - Manage metabolic abnormalities
 - Minimize AKI risk
 - Review dietary options
- Manage Comorbid**
 - Cardiovascular risk
 - Anemia management
 - Metabolic Bone Disease Management
- Prepare for ESRD**
 - Isolate high risk populations
 - Patient education
 - Refer to Nephrology
 - Prepare for angioaccess
 - Review Medical Management options

Diet and Lifestyle

Diet

- CKD patients should receive expert dietary advice if available
- Lower protein intake to 0.8 g/kg/day in patients with GFR <30 ml/min
- Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression.
- Target HbA1c of <7.0% (extended above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia)
- Lower salt intake to <2 g per day of sodium

Lifestyle

- Undertake physical activity
 - 30 minutes 5 times per week
- Achieve a healthy weight
 - BMI 20 to 25
- Stop smoking
- Avoid NSAID's

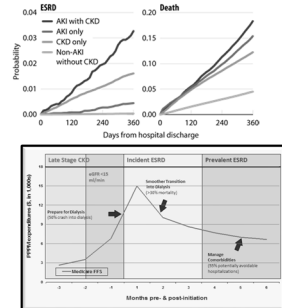
Vaccinations

- Annual Influenza
- Pneumococcal vaccine q 5 years
- Hepatitis B for stage 5 CKD and likely progression to HD

Kidney International Supplements (2013) 3, 5-14

CKD predisposes hospitalized patients to Acute Renal Failure

- CKD increases the risk of AKI seven fold in hospitalized patients.
- In AKI patients with CKD, the hazards for:
 - ESRD 85.0
 - Death 3.1
 (in AKI patients with no CKD, hazards are 11.7 and 2.5, respectively)



These are the patients who "crash" onto dialysis

USRDS ADR 2009

NephroPharmacology

Renally dose all medications and monitor eGFR and drug levels as indicated.

- Reconsider dose with any significant change in eGFR and review medications regularly for continued appropriateness.
- Prolonged NSAID use should be avoided in early stage CKD.
- Counsel patients to consult a physician or pharmacist before using over-the-counter medications or supplements.

Consider monitoring eGFR more frequently and holding renally cleared and potentially nephrotoxic medications during acute illness or in the perioperative period.

Imaging Studies

Iodinated Contrast Studies:

- Avoid high osmolar agents
- Use lowest possible contrast dose compatible with complete study
- Withdraw potentially nephrotoxic agents before and after the procedure
- Give adequate hydration with saline before, during, and after the procedure
- Measure GFR 48–96 hours after the procedure

Gadolinium-based contrast studies:

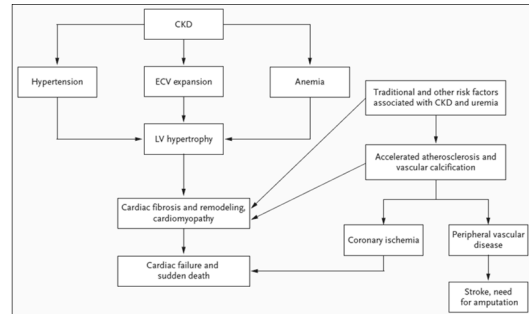
- Do not use gadolinium in Pts with GFR <15 ml/min/1.73 m² (unless there is no alternative appropriate test)
- For pts with a GFR <30 ml/min use a macrocyclic chelate preparation

Bowel preparation:

- Avoid oral phosphate-containing bowel preparations in pts with GFR <60 ml/min due to risk of phosphate nephropathy

Kidney International Supplements (2013) 3, v

Cardiovascular Disease in Patients with Chronic Kidney Disease



Abouad H and Henrich W. N Engl J Med 2010;362:56-65.

Management of HTN

JNC 8:

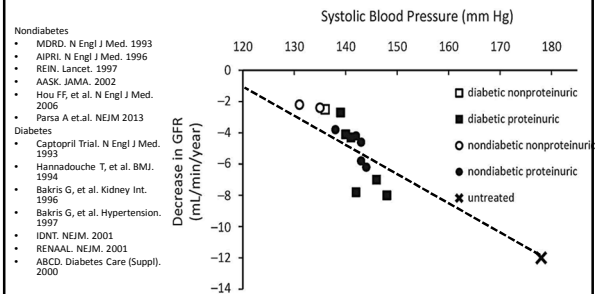
- In the general population aged ≥60 years
 - Treat BP > 150/90
- In the general population <60 years
 - Treat BP > 140/90
- In the population aged ≥18 years with CKD
 - Treat BP > 140/90 and use ACEI or ARB

KDIGO Guidelines:

- In diabetic and non-diabetic adults with CKD and with urine albumin excretion of >30 mg/24 hours
 - Treat BP >130/80 and use ACEI/ARB (2D level of evidence)

JAMA February 5, 2014 Volume 311, Number 5

Relationship Between Achieved BP and Decline in Kidney Function from Primary Renal Endpoint Trials



Update from Kalaitzidis R and Bakris GL. In: Handbook of Chronic Kidney Disease. Daugirdas J (Ed.) 2011.

Anemia Management

- Check hemoglobin in patients with eGFR < 45 ml/min
- Exclude other causes of anemia before attributing to CKD
- If the patient is likely to benefit in terms of quality of life, consider referral for ESA candidacy if Hb < 9g/dl

Studies of Anemia Management and the use of Erythropoietin in CKD

Normal Hct Study Besarab A et al. N Engl J Med 1998;339:584-590	183 deaths and 19 non fatal MI's in nl-Hct group and 150 deaths and 14 non fatal MI's in low-Hct group (RR 1.3; 95% CI, 0.9 to 1.9). Study halted.	Pts in nl-Hct group had a decline in the adequacy of dialysis and received more IV iron dextran.
CHOIR Study Ajay Singh et al. N Engl J Med 2006;355:2085-98.	125 events (Death, MI, CHF, Stroke) in the high-Hb group vs 97 events in the low-Hb group (HR, 1.34; 95% CI, 1.03 to 1.74; P = 0.03).	Improvements in the quality of life were similar in the two groups.
CREATE Study Drueke et al N Engl J Med 2006;355:2071-84	No effect on first cardiovascular event	General health and physical function improved significantly (P = 0.003 and P<0.001) in high Hb group.
TREAT Study Marc Pfeffer et al N Engl J Med 2009;361:2019-32	Death or a cardiovascular event in 632 pts in Rx group vs 602 pts in placebo group (P = 0.41)	Fatal or nonfatal stroke in 101 pts in Rx grp vs 53 in placebo group (P<0.001).

Vascular Biology is abnormal in CKD.

Coronary-Artery Calcification in Young Adults with End-Stage Renal Disease Undergoing Dialysis

(N Engl J Med 2000;342:1478-83. AIN May 1998 Vol 128:10; 839-847)



Sample electron-beam computed tomographic scan showing calcification of the left anterior descending coronary artery (thick arrow) and the aortic root (thin arrow).

1. Coronary-artery calcification is common and progressive in young adults with end-stage renal disease who are undergoing dialysis.
2. The mean serum phosphorus, the mean calcium-phosphorus ion product, and the daily intake of calcium were higher among the patients with coronary-artery calcification

Mineral Metabolism in CKD

Measure serum calcium and phosphate if eGFR < 45ml/min

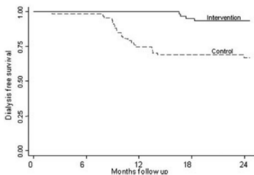
Avoid Hyperphosphatemia	Correct Nutritional 25OH Vit D Deficiency	Treat Secondary Hyperparathyroidism
Restrict dietary phosphate intake Use phosphate binders when indicated -Calcium based: CaCO ₃ ; Ca Acetate -Non Calcium Based Sevelamer; (AIOH3)	Supplement with 25OH Vit D if level <30ng/L Eg: Ergocalciferol 50000u/week for 12 weeks	Supplement 1,25 Vitamin D (Calcitriol) according to PTH level Treat with Calcitriol or equivalent if: - PTH > 70ng/L in CKD 3 - PTH > 120ng/L in CKD 4

Offer bisphosphonates for the prevention and treatment of osteoporosis in patients with eGFR > 30 ml/min on the same indications as for all other patients

Metabolic Acidosis

- Often becomes apparent at GFR <25-30 ml/min/1.73m².
- More severe with higher protein intake.
- May contribute to bone disease, protein catabolism, and progression of CKD.
- Correction of metabolic acidosis may slow CKD progression and improve patients functional status.

Adults with CKD 4 (eGFR 15-30) with bicarbonate 16-20 mmol/L; treated with sodium bicarbonate.

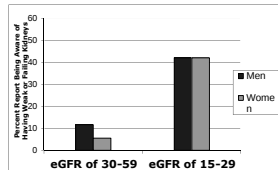


1) Mahajan, et al. Kidney Int. 2010;78:303-309.
2) de Brito-Ashurst I, et al. J Am Soc Nephrol. 2009;20:2075-2084.

Preparing for ESRD: Patient and Physician Awareness

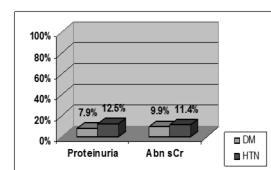
Patient awareness

Coresh, et al., 2007



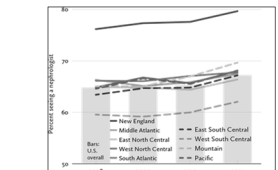
Physician Awareness

McClellan, AJKD 1997, 29:368-75



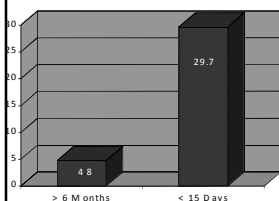
%Patients under Nephrology Care Prior To Dialysis Start

Peer Kidney Initiative

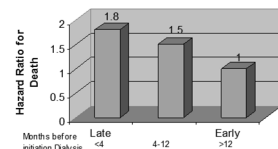


Preparing for ESRD: The Timing of Specialist Evaluation in Chronic Kidney Disease; effect on Morbidity and Mortality

Effect of timing of referral on length of stay at the initiation of dialysis

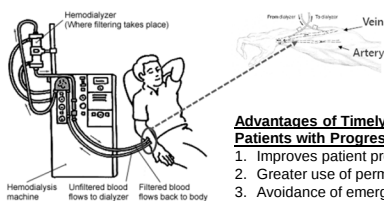


Rate of death measured from initiation of dialysis to average of 2.2 years follow up



Jungers et al, J Am Nephrol 1997; 8:140A
Kinchen et al Ann Intern Med. 2002;137:479-486.

Principle of Hemodialysis



Advantages of Timely Referral in Patients with Progressive CKD

1. Improves patient preparation for RRT.
2. Greater use of permanent vascular access.
3. Avoidance of emergent hemodialysis initiation.
4. Greater utilization of transplantation and self-care dialysis (i.e., peritoneal dialysis or home hemodialysis).
5. Management of medications which may help to delay the need for RRT.
6. Gives the nephrologist adequate time to counsel patients through this challenging transition in their lives.

Benefits of a Fistula

Diabetics:	Relative Risk	P value of death
AVF	1.00	
PTFE	1.39	0.0004
Catheter	1.49	0.0004

Non-Diabetics:	Relative Risk	P value of death
AVF	1.00	
PTFE	1.09	0.26
Catheter	1.72	0.0001

Thrombosis following PICC placement

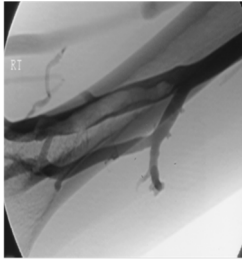


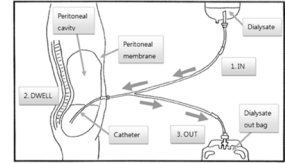
Figure 1. A 38-year-old asymptomatic woman 1 day after PICC placement with inadvertent removal. Venography demonstrates non-occlusive thrombus in a brachial vein

Allen et al, JIVR, 2000

- Identify CKD stages 3B,4 or 5, including current hemodialysis, peritoneal dialysis or transplant patients as a special population when planning central venous access
- Plan appropriate venous access in these cases
 - dorsal hand veins for phlebotomy
 - internal jugular veins are preferred for central venous access
 - external jugular veins are acceptable alternative
 - Avoid any catheters in subclavian veins

Peritoneal Dialysis

- Less than 8% of prevalent ESRD patients in the US are on PD; significantly less than in other developed countries
 - subtle differences in practice patterns
 - unintended financial considerations
- Medical outcome data would seem to favor more utilization of PD
 - Improved mortality
- Most home dialysis units are small
 - some have minimal clinical experience
 - consolidation of PD programs may be needed.

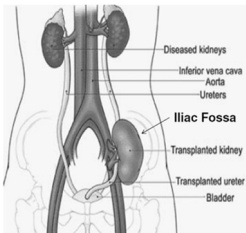


Multidisciplinary pre-dialysis programs increase the proportion of patients initiating dialysis with PD.

Burkhardt J, C-JASN 2009 Dec;4 Suppl 1:S125-31

Ribitsch et al Peritoneal Dial Int 2013 Jul-Aug;33(4):367-71

Kidney Transplantation

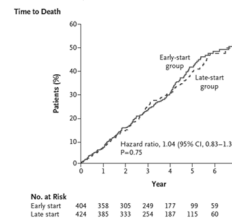


Key Concepts

- **Kidney transplantation is the most cost-effective modality of renal replacement.**
 - Transplanted patients have a longer life and better quality of life.
 - Early transplantation (before [pre-emptive] or within 1 year of dialysis initiation) yields the best results.
 - Living donor kidney outcomes are superior to deceased donor kidney outcomes.
 - Early transplantation is more likely to occur in patients that are referred early to nephrologists.
- **Refer for transplant evaluation when eGFR <20 mL/min/1.73m².**

Timing of the initiation of dialysis: Early versus Late Start.

- 828 patients
- Early Start: GFR 10-14ml/min; Late Start: GFR 5-7ml/min
- 76% of late start patients initiated HD with GFR>7.0ml/min



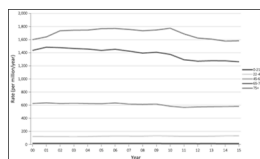
Consider dialysis initiation before/when one or more of following is present:

- Symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus);
- Inability to control volume status or blood pressure;
- Progressive deterioration in nutritional status refractory to dietary intervention;
- Cognitive impairment.

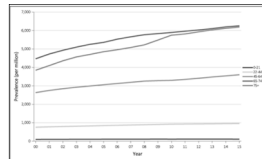
Often occurs in the GFR range between 7 and 10 ml/min

N Engl J Med 2010;363:609-19.

Incidence of ESRD: By Age - the ageing of the dialysis population



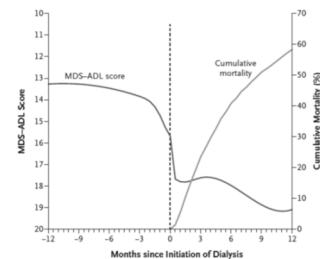
Trends in adjusted ESRD incidence rate, by age group, in the U.S. population, 2000-2015



Trends in the adjusted prevalence of ESRD, by age group, in the U.S. population, 2000-2015

USRDS ADR 2018

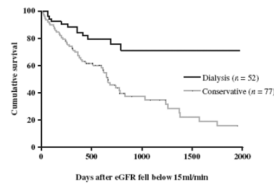
Functional Status of Elderly Adults before and after Initiation of Dialysis



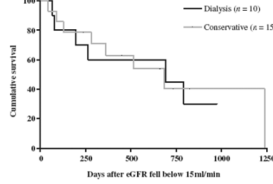
- 3702 nursing home residents in the United States
- Initiated dialysis between June 1998 and October 2000.
- At least one measurement of functional status was available before dialysis.
- Functional status was measured by assessing the degree of dependence in seven ADL's (on the Minimum Data Set-Activities of Daily Living [MDS-ADL] scale of 0 to 28 points, with higher scores indicating greater functional difficulty).

Tamura et al N Engl J Med 2009;361:1539-47.

A comparative survival study of patients over 75 years with chronic kidney disease stage 5



Kaplan-Meier survival curves comparing the dialysis and conservative groups ($P<0.001$).



Kaplan-Meier survival curves for those with high comorbidity (score ≥ 2), comparing dialysis and conservative groups

Murtagh et al Nephrol Dial Transplant (2007)

Conservative Management of Stage V CKD

- Conservative management should be an option
- It should be supported by a comprehensive management program.
- It should be available to people and families through either primary care or specialist care as local circumstances dictate.
- The comprehensive conservative management program should include:
 - protocols for symptom and pain management,
 - psychological care, spiritual care
 - culturally sensitive care for the dying patient and their family (whether at home, in a hospice or a hospital setting)
 - provision of culturally appropriate bereavement support.

Kidney International Supplements (2013) 3, 5–14

Conclusions

- Kidney Disease is common and management is complicated
- The majority of patients with CKD have non progressive disease
- Cardiovascular disease is a major co-morbidity
- For patients with progressive CKD care strategies should be initiated early to improve long term morbidity and mortality
- A team approach is required
- Pre-planning for renal replacement therapies is necessary in those with progressive disease

Cancer of the Renal Pelvis and Ureter

Vitaly Margulis, MD

Associate Professor
Department of Urology
UT Southwestern Medical Center

Disclosure:

Dr. Margulis has nothing to disclose

- Introduction
- Etiology
- Clinical Features
- Imaging Diagnosis
- Confirmatory Diagnosis
- Staging
- Risk stratification
- Treatment Guidelines
- Radical Nephroureterectomy
- Management of Bladder Cuff
- Lymphadenectomy
- Conservative Surgical Approaches
- Mx of upper tract positive cytology/CIS
- Adjuvant Therapy
- Treatment of Metastatic Disease
- Follow up protocol

Transitional Cell Carcinoma

- Originates from Transitional epithelium of urinary tract
- Most common in **urinary bladder**, then in renal pelvis, least in ureter(125:2.5:1)
- 5-10% of upper urinary tract neoplasms.
- Renal TCC most common --extrarenal part of the p followed by the infundibulocaliceal region
- 2%–4% ---bilaterally.

Relation with Bladder TCC

- Upper tract TCC after bladder TCC- 2-4%
- Bladder TCC after Upper tract TCC- 15-20%

ETIOLOGY

- Genetic
 - > Hereditary UTUC is associated with hereditary nonpolyposis colorectal carcinoma (HNPCC), or Lynch syndrome.
- Environmental
 - > Balkan Nephropathy/ Chinese herb nephropathy: Aristolochic acid, which is found in plants *Aristolochia fangchi* and *Aristolochia clematitis*, has a mutagenic action on codon 248 of p53 gene.
 - > Smoking: Aromatic amines.
 - > Analgesic abuse
 - Phenacetin- 2yrs latent phase
 - Acetoaminophen- 20 yrs latent phase.
 - > Arsenic exposure
 - > Occupational
 - 7 yrs of contact/inhalation to aromatic amines.

Clinical features

- ◉ most common in 7th decade, rare in childhood
- ◉ males 3 times > female

Clinical features

- ◉ Hematuria- gross/ microscopic- 56-95%
- ◉ flank pain or acute renal colic(clots)
- ◉ discovered incidentally at radiologic examination- 15%

IMAGING MODALITIES

INTRAVENOUS UROGRAPHY

- ◉ Supplanted by CT-IVU
- ◉ detailed anatomy of the pelvicalyceal system and ureters.

- ◉ a filling defect within the contrast-enhanced collecting system, single or multiple & smooth, irregular or stippled
- ◉ Stipple sign--tracking of contrast material into the interstices of a papillary lesion
- ◉ Tumor-filled, distended calyces --“oncocalyces.”
- ◉ If these fail to opacify with contrast-- “phantom calyces.”

Computed Tomography

- ◉ CT is well established in the preoperative staging and assessment of upper tract TCC- 100% sensitivity and 60%specificity.

CT urography

- ◉ single breath-hold coverage of the entire urinary tract,
- ◉ has improved resolution
- ◉ has the ability to capture multiple phases of contrast material excretion

- ◉ Hydronephrosis and hydroureter
- ◉ Ureteric TCC-- Ureteric wall thickening (eccentric or circumferential), luminal narrowing, or an infiltrating mass.
- ◉ A thickened enhancing ureteric wall with periureteric fat stranding -- suggestive of extramural spread

Pre-op Confirmation

- Cystoscopy – Mandatory to rule out concurrent bladder tumor.
- Ureteroscopy
 - Reserved for doubtful cases (On radiology)
 - Brush or punch biopsy
 - Staging not accurate as depth of tumor not well assessed
 - Risks of tumor seeding, extravasation, and dissemination- Low but present

Retrograde Pyelography

75% Sensitivity

- in inadequately excreting kidneys,
- in cases of contrast allergy.
- facilitates ureterorenoscopy with biopsy or brushing & cytology of urine
- an **intraluminal filling defect**,-- smooth, irregular, or stippled.

- An “**apple core**” appearance-- eccentric or encircling ureteric lesions
- localized ureteric dilatation around and distal to the filling defect may give rise to the “**goblet**” sign.

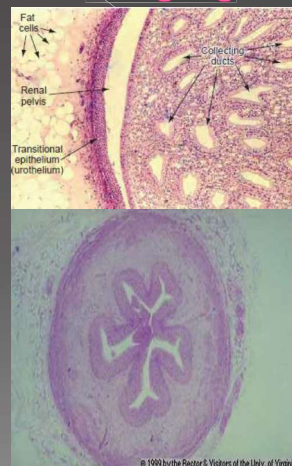
Cytology and Tumor Markers

- **Sensitivity**
 - 20% for grade 1 tumors
 - 45% for grade 2
 - 75% for grade 3 tumors
- If a voided cytology specimen is abnormal in a patient with an upper tract filling defect-
 - Ureteral catheterization
 - Washings from ureter more accurate
 - Brush biopsy- Sensitivity in the 90%
 - Massive hemorrhage
 - Perforation of the urinary tract with extravasation

FISH in TCC- Upper and Lower

- FISH probes were used for chromosomes 3, 7, 17, and the *CDKN2A* (9p21) gene, overall sensitivity of FISH was significantly higher than that of cytology and specificity for both was 100%

Staging



PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Ta	Papillary noninvasive carcinoma.
Tis	Carcinoma in situ.
T1	Tumor invades subepithelial connective tissue.
T2	Tumor invades the muscularis.
T3	Tumor invades periureteral fat (for renal pelvis only).
	Tumor invades beyond muscularis into perinephric fat or the renal parenchyma.
T4	Tumor invades adjacent organ or through the kidney into the perinephric fat.
LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases
N1	Metastasis to a single lymph node, 2 cm or less in greatest dimension.
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension.
N3	Metastasis in a lymph node, more than 5 cm in greatest dimension.
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis.

Histologically

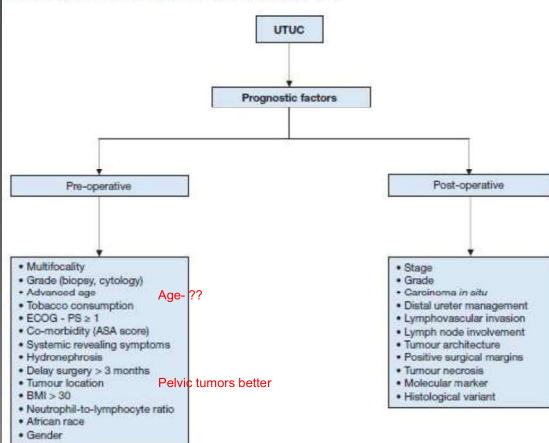
- TCC- Most common
- Variant Histology
 - Squamous- Ch. Infection, inflammation or analgesic abuse
 - Glandular
 - Sarcomatoid
 - Neuroendocrine
 - Micropapillary- Aggressive and poor prognosis

Tumor spreads by

- mucosal extension
- local
- Hematogenous
- lymphatic invasion
- The most common sites for metastases are the lungs, liver, bones, and regional lymph nodes.

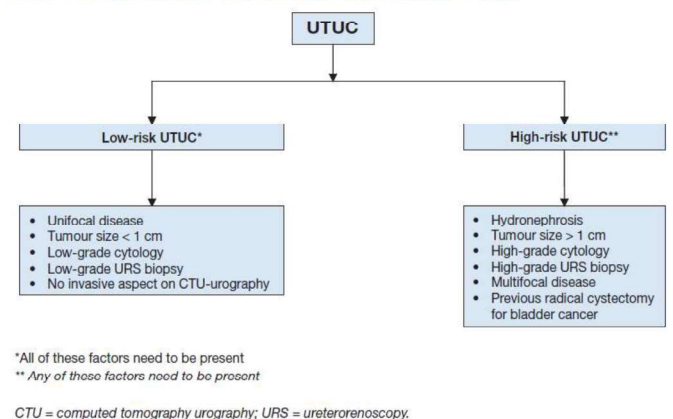
Prognostic Factors

Figure 6.1: Upper tract urothelial carcinoma - Prognostic factors

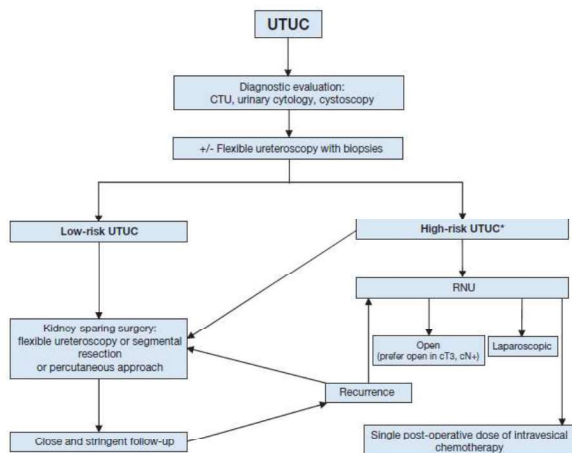


Risk Stratification

Figure 6.2: Pre-intervention risk stratification of upper tract urothelial carcinomas



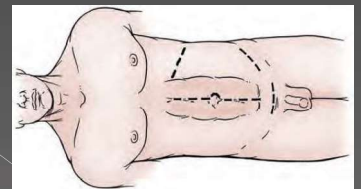
EUA GUIDELINES



CTU = computed tomography urography; RNU = radical nephroureterectomy.
*In patients with a solitary kidney, consider a more conservative approach.

Open Radical Nephroureterectomy

- Dissection outside gerota's
- Adrenal removed only if found involved on pre-op imaging or intra-operatively.
- Management of Distal Ureter and Bladder Cuff
 - The entire distal ureter, including the intramural portion and the ureteral orifice, has to be removed



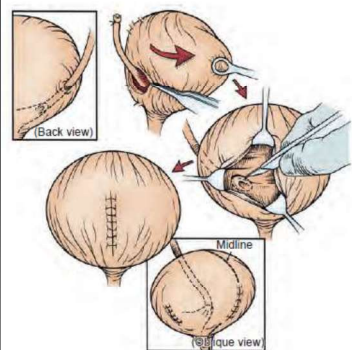
Management of Distal Ureter and Bladder Cuff

Importance of Complete Resection

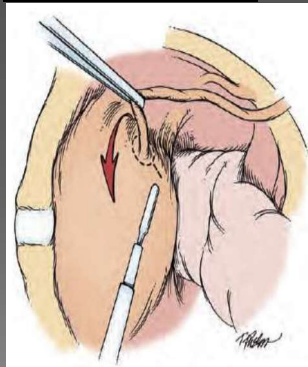
- The risk of tumor recurrence in a remaining ureteral stump is 30% to 75%

Traditional Open Distal Ureterectomy

Intravesical Approach

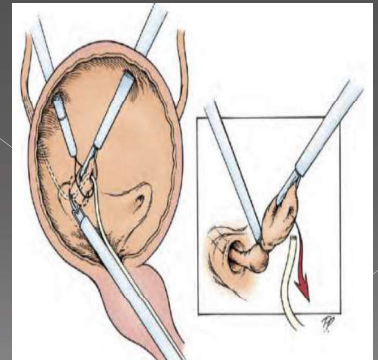


Extravesical Approach



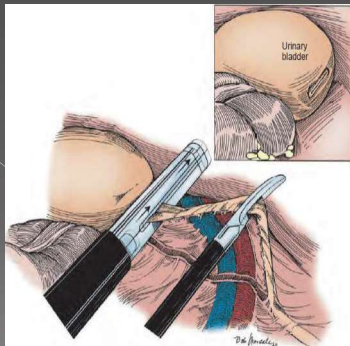
Transvesical Ligation and Detachment Technique

- Low lithotomy position
- Cystoscopy- bladder filled.
- One or two 5-mm trocars are placed intravesically from the suprapubic area.
- Endoloop is placed around the ureteral orifice, and a ureteral catheter is advanced into the ureter through the Endoloop.
- With a Collins knife the bladder cuff is incised, and this incision is carried into the extravesical space.
- Retraction is provided by the grasper through one of the trocars.
- Once the ureter is freed, the Endoloop is cinched around the ureter as the catheter is removed.



Total Laparoscopic Technique

- Initial cystoscopy - Placement of a ureteral catheter and incision of an intramural tunnel at the 12 o'clock position Ureteral orifice is cauterized
- After nephrectomy the distal ureter is traced to detrusor muscle. The detrusor muscle is split and the ureter retracted in antegrade direction. The endovascular stapler is then used to place a staple line as distally as possible.
- A fulguration mark helps serve as an identifier of the bladder cuff
- Potential for leaving ureter mucosa within the staple line – Contraindicated in distal ureteral tumors.

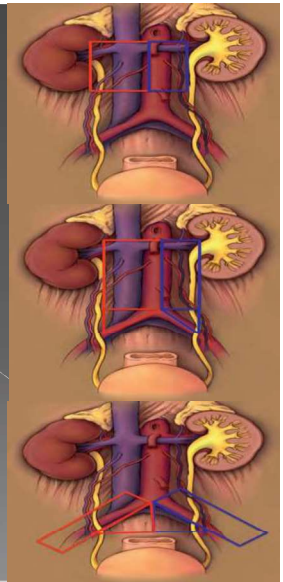


Lymphadenectomy

The role and extent of lymphadenectomy

- Limited or regional lymphadenectomy is included with radical nephroureterectomy

- **For renal pelvis-** Ipsilateral hilar nodes +
 - Right-sided tumors - paracaval, retrocaval, and interaortocaval lymph nodes
 - For left sided tumors- para-aortic lymph nodes
 - The inferior mesenteric artery marks the inferior boundary of the template.
- **For upper two thirds of the ureter-** Template is extended to the level of bifurcation of aorta
- **For distal ureter-** Ipsilateral common, external and internal iliac, obturator, and presacral nodes.



Conservative Approaches

Open Nephron-Sparing Surgery for Renal Pelvis Tumors

- The risk of recurrence after conservative surgery
 - Grade 1 - less than 10%
 - Grade 2- 28%
 - Grade 3 - 60%

Open Segmental Ureterectomy

- Ureteroureterostomy
 - Proximal ureter or mid-ureter
 - 1-2 cm margin proximally and distally
- Distal Ureterectomy and Direct Neocystostomy or Ureteroneocystostomy with a Bladder Psoas Muscle Hitch or a Boari Flap
- Ileal Ureteral Replacement
- Renal autotransplantation

- **Segmental ureterectomy is offered for low-grade, non-muscle-invasive disease of the proximal ureter or mid-ureter that is not amenable to complete ablation by endoscopic means because of tumor size or multiplicity.**
- **Distal ureterectomy and neocystostomy may be offered for low-grade, low-stage, or in select cases, high-grade, locally invasive tumors of the distal ureter when renal preservation is necessary.**

Open v/s Endoscopic Management

- The advantage of a ureteroscopic approach is lower morbidity than that of the percutaneous and open surgical counterparts, with the maintenance of a closed system.
- With a closed system, nonurothelial surfaces are not exposed to the possibility of tumor seeding.

Endoscopic Management

- Indications
 - > Unifocal Disease
 - > Low Grade tumor
 - > Low volume tumor < 1cm
 - > Non invasive on CT- IVU
 - > Abnormal kidney – Opposite
 - Bilateral tumor
 - CKD
 - Higher risk for CKD
 - > Poor surgical risk

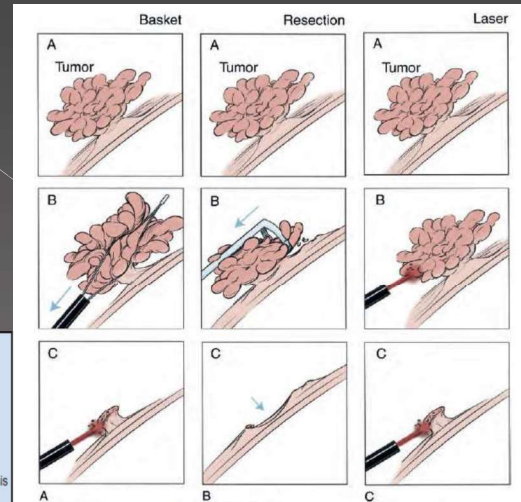
Antegrade v/s Retrograde Mx

- Retrograde
 - > Smaller instruments - smaller field of view and working channel- Removal of bulky tumors not possible
 - > Difficulty in accessing the lower pole
 - > Difficult in patients with prior urinary diversion.
- Percutaneous
 - > Large volume tumor can be resected
 - > Higher morbidity
 - > Better in complicated calyceal and lower pole calyx
 - > Nephrostomy tract can be maintained for immediate postoperative nephroscopy and administration of topical adjuvant therapy

Endoscopic Resection

Ho:YAG
Minimal penetration (<0.5 mm)
Efficient ablation of tumor
Precise cutting
Setting 0.6-1.2 joules/8-10 Hz

Nd:YAG
Deep penetration (5-6 mm)
Excellent hemostasis
Tumor ablation by coagulative necrosis
Settings: 20-30 watts

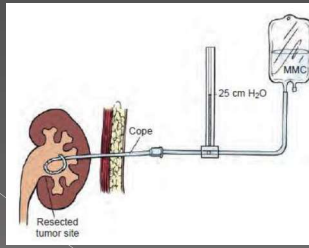


Adjuvant Therapy

- After Organ-Sparing Therapy
 - > Instillation Therapy
 - Immunotherapeutic Agent
 - Chemotherapeutic Agent
- After Complete Excision
 - > Radiation Therapy
 - > Systemic Chemotherapy

After Organ-Sparing Therapy

- **Instillation Therapy**- Primary treatment for CIS and as adjuvant therapy after endoscopic or organ-sparing therapy.
 - **Thiotepa**
 - **Mitomycin**
 - **BCG**
 - Gemcitabine alternative to BCG with fewer side effects.
- **Brachytherapy**- To nephrostomy tract through iridium wire or delivery system- described by Patel and coworkers (1996) and Nurse and colleagues (1989). No recurrences. Complication- Cutaneous fistula formation requiring nephroureterectomy.



- 1: Nephrostomy tube
- 2: Ureteric catheter
- 3: Ureteral stent or by iatrogenically created vesicoureteral reflux- Not reliable

After Complete Excision

- **Radiation Therap**
 - For Stage T3 to T4, N+
 - Radical nephroureterectomy alone provides a high rate of local control. Adjuvant radiation without chemotherapy for high-stage disease does not protect against a high rate of distant failure.
 - There may be a role for combined radiation-chemotherapy regimens in patients with advanced disease with adverse features; however, the current evidence supporting this is small and retrospective in nature.

- Systemic Chemotherapy
- Neo-adjuvant:
 - MVAC (methotrexate, vinblastine, Adriamycin, and cisplatin),
 - MEC (methotrexate, etoposide, and cisplatin)
 - MVEC (methotrexate, vinblastine, epirubicin, and cisplatin)
 - gemcitabine-paclitaxel-doxorubicin [GTA]
 - Cisplatin-gemcitabine[GC]
- Adjuvant Chemotherapy
- **Lack of controlled trials that establish the efficacy of either neoadjuvant or adjuvant chemotherapy in this UTUC. However, given the significant influence of renal function on eligibility to receive effective chemotherapy, the focus is shifting toward a neoadjuvant approach, with several trials underway.**
- Further studies are needed to aid in providing recommendations in this setting.

Follow up protocol for Low Risk Disease

- Physical examination, urine cytology (only for high-grade lesions), and cystoscopy
 - Every 3 months—first year
 - Every 6 months thereafter—years 2 through 3
 - Yearly—thereafter
- Contralateral imaging (IVU or retrograde pyelography)—yearly
- Ipsilateral endoscopy (patients undergoing organ-sparing therapy)—
 - Every 6 months—first several years
 - Yearly—thereafter

Follow up protocol for High Risk Disease

- **Metastatic evaluation—necessary in all patients with significant risk of disease progression (i.e., high grade or invasive disease)**
 - Physical examination, chest x-ray, comprehensive metabolic panel with liver enzymes
 - Every 3 months—first year
 - Every 6 months—years 2 through 3
 - Yearly—years 4 and 5
 - After 5 years—evaluation of urothelium only
 - Computed tomography or MRI of abdomen and pelvis—
 - Every 6 months—years 1 and 2
 - Yearly—years 3 through 5
 - Bone scan—only for elevated alkaline phosphatase level or symptoms of bone pain

Treatment of Metastatic Disease

- When there is evidence of regional lymph node metastases, initial chemotherapy should be given as the primary therapy, and surgery should be withheld until a good—ideally a complete—radiographic response is seen. At that time, consolidative surgery can be offered.
- Paclitaxel, cisplatin, and gemcitabine (PCG) versus gemcitabine and cisplatin (GC)- Better survival with addition of paclitaxel
- Carboplatin is frequently substituted for cisplatin because of either limitations of renal function or concerns over toxicity with the latter, but the results with carboplatin remain inferior.
- Upcoming molecule- Cabozantinib, the inhibitor of MET and VEGF pathways

Thank You

Evaluation and Medical Management of OAB and Urinary Incontinence

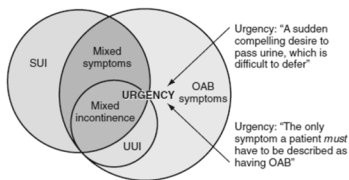
Gary E. Lemack, M.D.
Professor and Residency Program Director
UT Southwestern Department of Urology



Disclosures

- Consultant for Allergan, Astellas, Avadel, GTx, Urovant, Blue Wind

Spectrum of Urinary Incontinence and OAB



Campbell's Urology

Types of Urinary Incontinence

- **Urgency**
 - urine loss accompanied by urgency
 - **Stress**
 - urine loss resulting from sudden increased intra-abdominal pressure (eg, laugh, cough, sneeze)
 - **Mixed symptoms**
 - combination of stress and urge incontinence
-
- Sudden increase in intra-abdominal pressure
→ Detrusor overactivity
→ Altered sensation
→ Urethral pressure

Differential Diagnosis: OAB and Stress Incontinence

Medical History and Physical Examination

Symptom Assessment

Symptoms	Overactive bladder	Stress incontinence
Urgency (strong, sudden desire to void)	Yes	No
Frequency with urgency (>8 times/24 h)	Yes	No
Leaking during physical activity; eg, coughing, sneezing, lifting	No	Yes
Amount of urinary leakage with each episode of incontinence	Large (if present)	Small
Ability to reach the toilet in time following an urge to void	Often no	Yes
Waking to pass urine at night	Usually	Seldom

Abrams P, Wein AJ. The Overactive Bladder: A Widespread and Treatable Condition. Erik Sparre Medical AB; 1998.

Evaluation – Stress Urinary Incontinence

AUA/SUFU Guidelines Statements 1-3

PATIENT EVALUATION: GOALS

- Confirm SUI
- Optimally characterize incontinence
- Assess differential diagnosis
- Consider impact of coexisting conditions
- Aid in treatment selection
- Determine prognosis

PATIENT EVALUATION

1. In the initial evaluation of patients with stress urinary incontinence desiring to undergo surgical intervention, physicians should include the following components: (Clinical Principle)

- Focused history, including assessment of bother
- Focused physical examination, including a pelvic examination
- Objective demonstration of stress urinary incontinence with a comfortably full bladder (any method)
- Assessment of post-void residual urine (any method)
- Urinalysis

PATIENT EVALUATION

The history, bladder diary, questionnaires, and/or pad testing should yield:

PATIENT EVALUATION

Physical examination of SUI patients should include:

- Focused abdominal examination
- Evaluation of urethral mobility (any method)
- Supine and/or standing stress test with comfortably full bladder
- Assessment of pelvic prolapse (any method)
- Assessment of vaginal atrophy/estrogenization status
- Focused neurologic examination

Diagnostic evaluation should include:

- Urinalysis
- PVR

PATIENT EVALUATION

2. Physicians should perform additional evaluations in patients being considered for surgical intervention who have the following conditions: (Expert Opinion)

- Inability to make definitive diagnosis based on symptoms and initial evaluation
- Inability to demonstrate stress urinary incontinence
- Known or suspected neurogenic lower urinary tract dysfunction
- Abnormal urinalysis, such as unexplained hematuria or pyuria
- Urgency-predominant mixed urinary incontinence
- Elevated post-void residual per clinician judgment
- High grade pelvic organ prolapse (POP-Q stage 3 or higher) if SUI not demonstrated with pelvic organ prolapse reduction
- Evidence of significant voiding dysfunction

PATIENT EVALUATION

3. Physicians may perform additional evaluations in patients with the following conditions: (Expert Opinion)

- Concomitant overactive bladder symptoms
- Failure of prior anti-incontinence surgery
- Prior pelvic prolapse surgery

CYSTOSCOPY & URODYNAMICS

Guidelines Statements 4-6

CYSTOSCOPY & URODYNAMICS TESTING

4. Physicians should not perform cystoscopy in index patients for the evaluation of stress urinary incontinence unless there is a concern for urinary tract abnormalities. (Clinical Principle)
5. Physicians may omit urodynamic testing for the index patient desiring treatment when stress urinary incontinence is clearly demonstrated. (Conditional Recommendation; Evidence Level: Grade B)

CYSTOSCOPY & URODYNAMICS TESTING

Table 3. Clinical Diagnosis.*

Diagnosis	After Office Evaluation Urodynamic- Testing Group (N=315)	Evaluation- Only Group (N=315)	P Value	After Urodynamic Testing (N=294)†	P Value‡
Stress urinary incontinence — no. (%)	315 (100)	315 (100)	>0.99	292 (99.3)	NA
Overactive bladder with incontinence — no. (%)	131 (41.6)	108 (34.3)	0.06	74 (25.2)	<0.001
Overactive bladder without incontinence — no. (%)	99 (31.4)	94 (29.8)	0.67	61 (20.7)	0.002
Voiding dysfunction — no. (%)	7 (2.2)	9 (2.9)	0.61	35 (11.9)	<0.001
Suspected intrinsic sphincter deficiency — no. / total no. (%)§	61/314 (19.4)	54/315 (17.1)	0.46	37/294 (12.6)	0.003

* Physicians completed a checklist of five possible diagnoses, which were not considered to be mutually exclusive. NA denotes not applicable.

† Data on diagnoses are for the urodynamic-testing group only and were missing for 21 women in this group.

‡ P values are for the comparison of diagnoses before and after urodynamic testing.

§ Data on the diagnosis of suspected intrinsic sphincter deficiency were missing for 1 woman in the urodynamic-testing group.

Nager 2012

CYSTOSCOPY & URODYNAMICS TESTING

6. Physicians may perform urodynamic testing in non-index patients. (Expert Opinion)

Urodynamic testing may be performed at the urologist's discretion in certain non-index patients to facilitate diagnosis, treatment planning, and counseling:

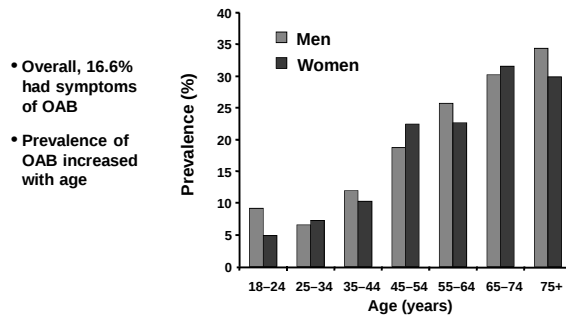
Overactive Bladder and Urgency Incontinence

National Overactive Bladder Evaluation (NOBLE) Program

- Large US prevalence study for OAB
 - November 2000–January 2001
 - 17,231 households contacted
 - 5,204 completed interviews
 - 4,160 controls, 1,044 cases
- Conclusions
 - Over 33 million OAB sufferers (16.6% of population)
 - 63% OAB dry; 37% OAB wet
 - OAB significantly impairs health related quality of life, even in those without urge incontinence

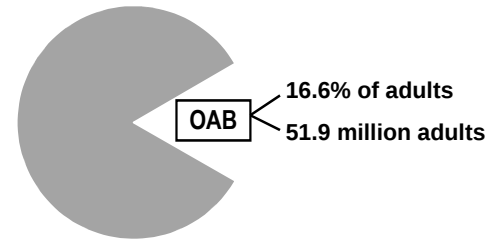
Adapted from Stewart WF et al. *World J Urol.* 2003;20:327-336.

Prevalence of OAB in the US



Adapted from Stewart W et al. *World J Urol.* 2003;20:327-336.

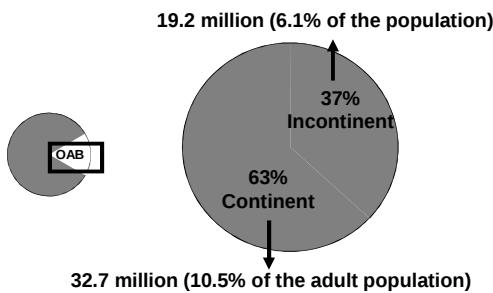
NOBLE: US Prevalence of Overactive Bladder



US Population ≈ 313 million adults

Stewart W et al. Prevalence of OAB in the US: results from the NOBLE program. Poster presented at WHO/ICI; July, 2001; Paris, France.

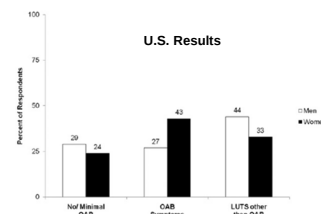
Prevalence of Overactive Bladder: Incontinent versus Continent



Stewart W et al. Prevalence of OAB in the US: results from the NOBLE program. Poster presented at WHO/ICI; July, 2001; Paris, France.

EpiLUTS Survey

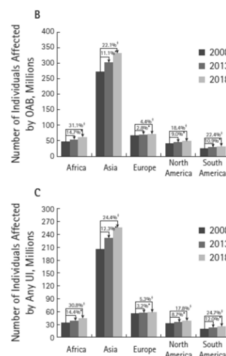
62,301 men and women emailed a survey of 106 questions – 31,588 responded, 20,000 randomly selected (similar # of men and women) in UK, Sweden, USA. Mean age 55.



Strongest predictor of bother associated with OAB was urinary urgency followed by UII

Milson I et al *Urology* 2012; 80: 90-96

Worldwide OAB estimates

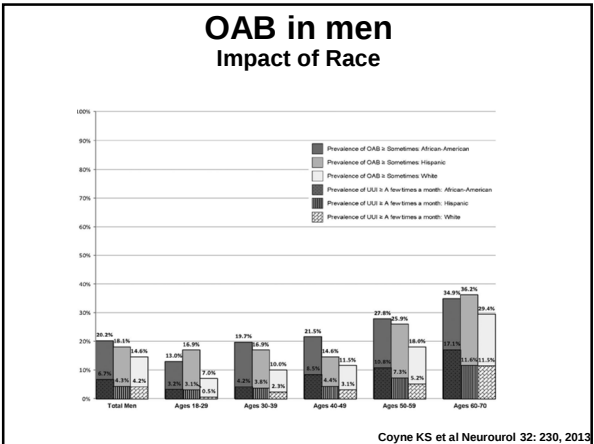
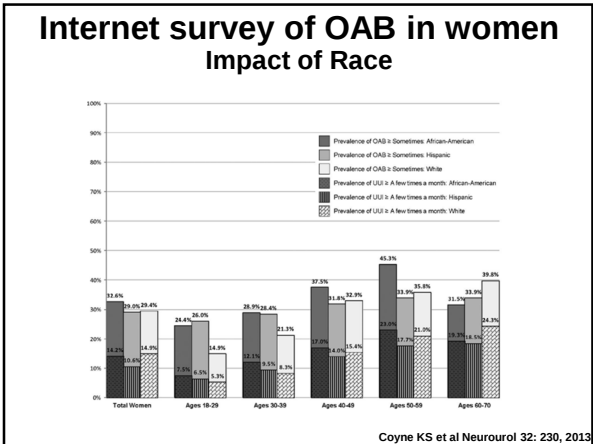


Irwin DE et al *BJUI* 2011; 108:1132.

Incontinence Risk Factors/Associations

- Aging
- # Pregnancies
- Being pregnant
- # Vaginal deliveries
- Large Birth Weight
- Prolonged labor
- Diet
- Obesity
- Diabetes
- Depression
- Race
- Ethnicity
- Residency in long term health care facility

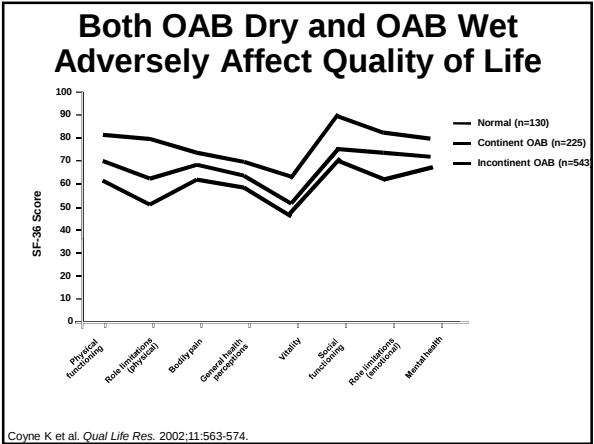
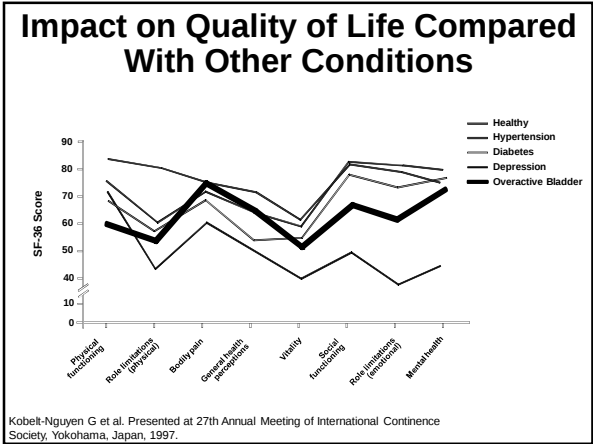
Lemack and Anger *Campbells* 2014



Relationship of OAB to other medical conditions

Characteristic	Cases	Controls
No. of participants	1434	1434
Mean (sd) age, years	53.8 (16.4)	53.7 (16.5)
n (%):		
Medical comorbidities (n sample)		
Chronic constipation (2863)	88 (6.2)	34 (2.4)
Asthma (2866)	167 (11.7)	106 (7.4)
Diabetes (2865)	128 (8.9)	87 (6.1)
High blood pressure (2862)	418 (29.3)	325 (22.7)
Bladder or prostate cancer (2828)	37 (2.6)	14 (1.0)
Neurological conditions*	58 (4.0)	16 (1.1)
Depression (2866)	221 (15.4)	100 (7.0)

Coyne KS et al BJUI 2008; 101, 1388

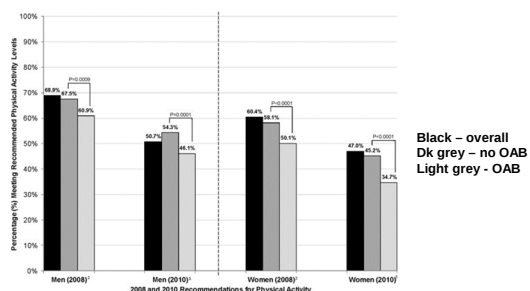


OAB diminishes Quantity and Quality of Sex

- Survey of over 14000 men and women comparing those with OAB to those with no LUTS
- OAB was strongest predictor of diminished sexual activity and significantly less enjoyment of sex ($p < .00001$)
- Interestingly, being from Sweden (vs US), having IC, Neuro condition, *Younger* age, depression and anxiety ALL associated with less sex.
- OAB also predictor of ED in men

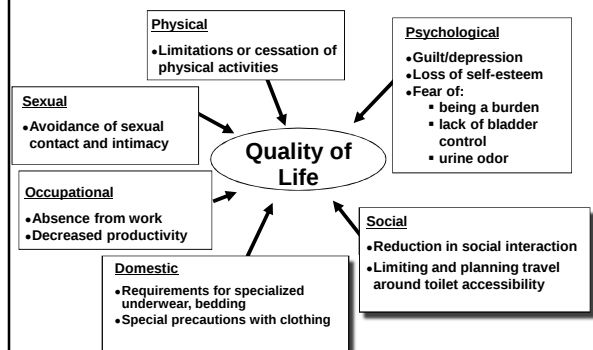
Coyne KS et al J Sex Med 8: 1603, 2011

Patients with OAB are less Physical Activity



Coyne KS et al Urology 82: 799, 2013

Impact of OAB on Quality of Life



Making a diagnosis of OAB

Diagnosis of OAB

- A presumptive diagnosis of OAB can be based on
 - patient history, symptom assessment
 - physical examination
 - Urinalysis → if positive MUST initiate workup
- Initiation of noninvasive treatment may not require an extensive further workup

Gormley EA et al J Urol 188: 2455, 2012

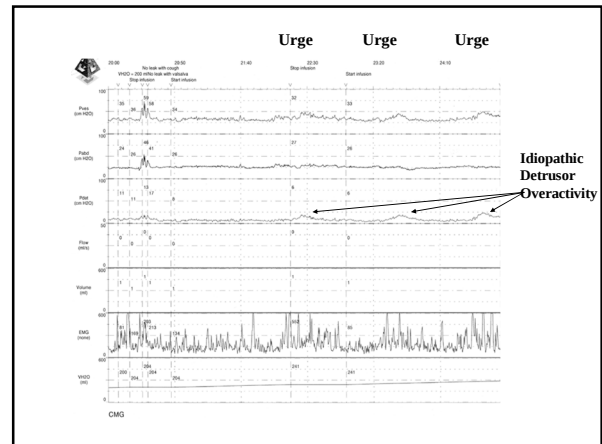
Other causes of OAB symptoms

A shortened list...

- Pelvic Organ Prolapse
 - Interstitial Cystitis
 - Urinary tract infection
 - Carcinoma in situ
 - Bladder outlet obstruction
 - Polyuria
 - Sleep disturbances
 - Medication induced
- IF any of these diagnoses are suspected then additional workup is suggested

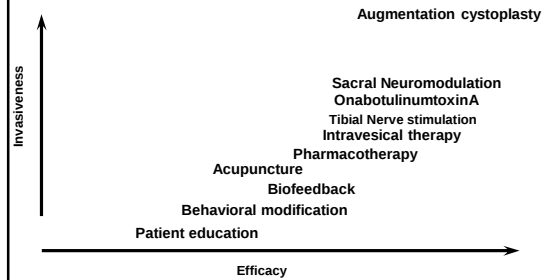
What other testing – BE SELECTIVE

- Post void residual
- Urinary flow rate
- Cystoscopy
- Upper urinary tract imaging
- Lower urinary tract imaging
- Urodynamic testing

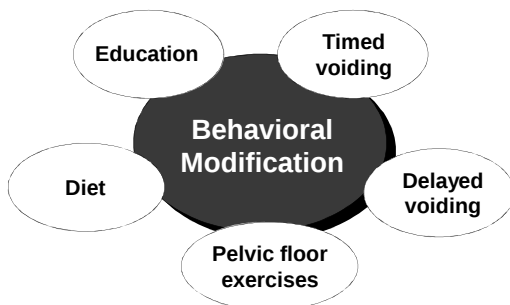


Management of OAB

Treatment strategies



Nonpharmacologic Treatments



Behavioral Modification



Combined Behavioral and Drug Therapy for Urge Incontinence

“Whether drug and behavioral therapy are combined from the onset or used sequentially in a stepped program, the evidence from the present study is that two interventions combined have a greater potential to enhance outcome than could be achieved by either intervention alone.”

Burgio K et al. J Am Geriatr Soc. 2000;48:370-374.

Diet Modification

- Daily fluid intake
 - reduce nighttime fluids to manage nocturia
- Eliminate bladder irritants such as:
 - caffeine
 - alcohol
 - nicotine
- Evaluate and modify bowel habits as appropriate
 - add fiber to diet

Behavior Modification

- When the urge strikes:
 - Stop and stay still
 - Squeeze pelvic floor muscles
 - Relax rest of body
 - Concentrate on suppressing urge
 - Wait until the urge subsides
 - Walk to bathroom at normal pace

Other therapies

- Vaginal estrogen
 - Proven efficacy in reducing recurrent UTI's in postmenopausal females
 - Appropriate for symptoms related to atrophic vaginitis
 - NOT consistently shown to have benefit for OAB (may worsen LUTS)

Antimuscarinic Agents

- Tolterodine (Detrol® LA)
- Oxybutynin (Ditropan XL®, Gelnique®)
- Trospium (Sanctura®)
- Solifenacin (Vesicare®)
- Darifenacin (Enablex®)
- Fesoterodine (Toviaz®)

Oxybutynin Ditropan

- Available for over 35 years
- Initially prescribed for GI related effects
- No agent has superior efficacy
- Side effect profile may be more pronounced
 - Cognitive dysfunction in frail/vulnerable
 - Constipation an issue in those on multiple meds

Trospium Chloride Sanctura

- Quarternary amine
 - All others tertiary amines
 - May impact ability to cross blood brain barrier
- Equal affinity for M2 and M3 receptors
- Minimally metabolized by CYP450 system
- 60% of drug excreted in urine minimally metabolized

Solifenacin succinate Vesicare

- Competitive muscarinic receptor antagonist
- No food effect
- Highly (~98%) bound to plasma protein (α_1 -acid glycoprotein)
 - No significant drug-drug interactions with digoxin
- Metabolized (primarily by CYP3A4) in the liver
 - Alternate metabolic pathways exist
 - No significant drug-drug interactions with warfarin or oral contraceptives
- $t_{1/2}$ of ~50 hours (range 45-68)

Darifenacin Enablex

- M3 selective muscarinic receptor antagonist
- Metabolized primarily by P450 enzymes
 - CYP2D6
 - CYP 3A4
- No dose adjustment for renal insufficiency
- Dose adjust for moderate hepatic impairment
 - Don't exceed 7.5 mg

Fesoterodine Toviaz

- Structurally related to tolterodine
- Parent compound has no affinity to muscarinic receptor
- Metabolized immediately by serum esterases
- Serum levels predictable (more so than tolterodine), allowing dose increases. No "poor metabolizers"
- Dose adjustments for severe renal/liver impairment.

Antimuscarinics

Generic Name	Trade Name	Available Doses	Mode of Delivery	Year Approved
Oxybutynin	Ditropan®	IR: 2.5 mg; 5 mg	Oral (tids)	1975
	Ditropan XL®	ER: 5 mg; 10 mg	Oral (qd)	1999
	Oxytrol	36 mg/patch (3.9 mg/d)	Transdermal	2008
	Gelnique	10% gel	Transdermal	2009
Tolterodine	Detrol®	IR: 1 mg; 2 mg	Oral (qd)	1998
	Detrol LA®	ER: 2 mg; 4 mg	Oral (qd)	2001
Trospium	Sanctura®	20 mg	Oral (qd)	2004
Solifenacin	Vesicare®	5 mg; 10 mg	Oral (qd)	2005
Darifenacin	Enablex®	7.5 mg; 15 mg	Oral (qd)	2005
Propiverine	Detrunorm	15 mg	Oral (qd)	2006
Fesoterodine	Toviaz™	4 mg; 8 mg	Oral (qd)	2009

Antimuscarinics: Efficacy

- A meta-analysis of the effects of antimuscarinics in OAB has confirmed:
 - Antimuscarinics are efficacious
 - Greater proportions of patients treated with antimuscarinics than with placebo returned to continence
 - Antimuscarinics were more effective than placebo for mean change in the:
 - Number of incontinence episodes per day
 - Number of micturitions per day
 - Number of urgency episodes per day
 - Volume voided per micturition
 - Profiles of each drug and dosage differ

Chapple C, et al. Eur Urol. 2008;54:543-562.

Antimuscarinics: Tolerability

- In a meta-analysis:
 - Dry mouth is the most commonly reported adverse event (29.6% on treatment vs 7.9% on placebo), followed by pruritus (15.4% on treatment vs 5.2% on placebo), constipation, headache and abnormal vision
- Tolerability may limit persistence
 - Studies have shown that 6-month cumulative discontinuation rate for antimuscarinics in women is high at 59%
 - The median time to discontinuation of antimuscarinics in that study was 4.76 months

Chapple C, et al. *Eur Urol*. 2008;54:543-562.
Gopal M et al. *Obstet Gynecol*. 2008;112:1311-1318

Cumulative Use of Strong Anticholinergics and Incident Dementia A Prospective Cohort Study

Shelly L. Gray, PharmD, MS; Melissa L. Anderson, MS; Sascha Dublin, MD, PhD; Joseph T. Hanson, PharmD, MS; Rebecca Hubbard, PhD; Rod Walker, MS; Onchee Yu, MS; Paul K. Crane, MD, MPH; Eric B. Larson, MD, MPH

- Prospective study
- 3434 participant (1994-1996, 2000-2003)
- 65 years old with no dementia at entry
- Computerized pharmacy dispensing data to calculate total standardized daily dose of anticholinergics (TSDDs) in the past 10 years
- Most recent 12 month data excluded to avoid possibility of acute mental status changes

JAMA Intern Med. 2015;175(3):401-407.



From: Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study

JAMA Intern Med. 2015;175(3):401-407. doi:10.1001/jamainternmed.2014.7663

Table 3. Association of Incident Dementia and AD With 10-Year Cumulative Anticholinergic Use*

Diagnosis, TSDD ^b	Follow-up Time, Person-years	No. of Events	HR (95% CI)	
			Unadjusted ^{c,d}	Adjusted ^{e,f,g}
Dementia				
0	5618	136	1 [Reference]	1 [Reference]
1-90	7704	203	0.96 (0.77-1.20)	0.92 (0.74-1.16)
91-365	5051	172	1.31 (1.04-1.65)	1.19 (0.94-1.51)
366-1095	2626	102	1.39 (1.07-1.82)	1.23 (0.94-1.62)
>1095	4022	184	1.77 (1.40-2.23)	1.54 (1.21-1.96)
AD				
0	5618	112	1 [Reference]	1 [Reference]
1-90	7704	168	0.96 (0.75-1.24)	0.95 (0.74-1.23)
91-365	5051	128	1.21 (0.93-1.58)	1.15 (0.88-1.51)
366-1095	2626	83	1.38 (1.01-1.85)	1.30 (0.96-1.76)
>1095	4022	146	1.73 (1.34-2.24)	1.63 (1.24-2.14)

Abbreviations: AD, Alzheimer disease; HR, hazard ratio; TSDD, total standardized daily dose.

* Observations with missing adjustment variables are excluded from the model (115 observations [3.3%]).

^b Calculation of the TSDD is described in Table 1.

^c Adjusted for age via the time axis.

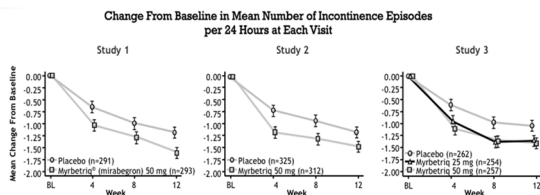
^d $P < .001$ test for trend, for an association between exposure categories and each outcome.

^e Adjusted for Adult Changes in Thought (ACT) study cohort, age (via the time axis), age at entry into the ACT study, sex, educational level, body mass index, current smoking, regular exercise, self-rated health, hypertension, diabetes mellitus, stroke, coronary heart disease, Parkinson disease, history of depressive symptoms, and current benzodiazepine use.

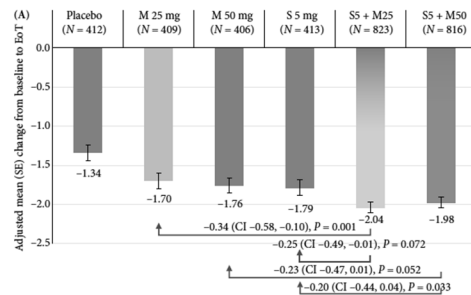
Mirabegron Myrbetriq

- Beta-3 agonist
- Once daily dosing – 25, 50 mg
- Minimal anticholinergic type side effects
- HTN closely assessed, minimal impact seen
- Avoid in those with poorly controlled HTN
- Efficacy similar to anti-muscarinic agents
- May be preferable in patients with heavy anticholinergic load

Mirabegron - efficacy



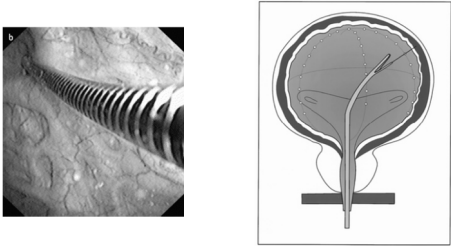
Mirabegron + Solifenacin



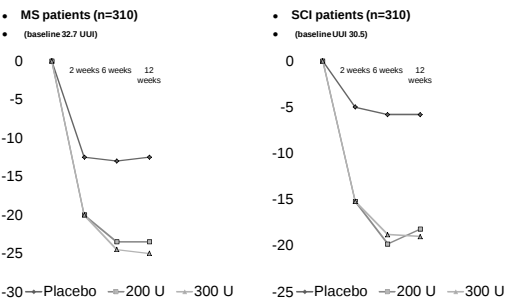
Herschorn S et al BJU120: 562, 2017

Refractory OAB:
What to do if medications fail?

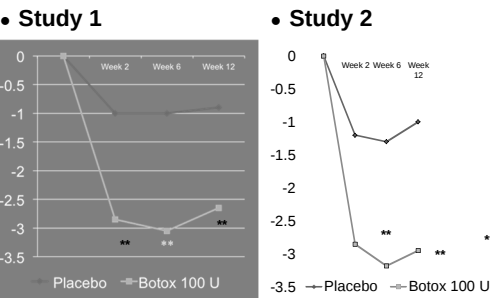
OnaotulinumtoxinA (Botox)



Change in UII – Neurogenic pts
Botox



Changes in UII – OAB pts
Botox

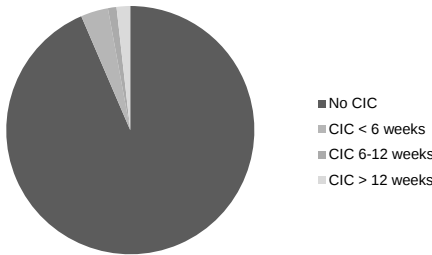


Adverse events

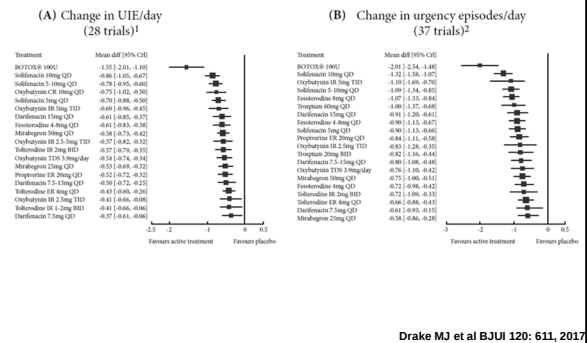
Adverse event	First 12 wk		Entire treatment cycle	
	Placebo, n = 270	OnabotA 100 U, n = 274	Placebo, n = 270	OnabotA 100 U, n = 274
AEs with incidence > 3%, no. (%)				
UTI	14 (5.2)	56 (20.4)	26 (9.6)	66 (24.1)
Dysuria	10 (3.7)	16 (5.8)	11 (4.1)	16 (5.8)
Bacteriuria	6 (2.2)	10 (3.6)	9 (3.3)	17 (6.2)
Urinary retention	1 (0.4)	16 (5.8)	1 (0.4)	16 (5.8)
Haematuria	1 (0.4)	10 (3.6)	2 (0.7)	10 (3.6)
Leukocyturia	2 (0.7)	7 (2.6)	2 (0.7)	10 (3.6)
Residual urine volume	1 (0.4)	8 (2.9)	2 (0.7)	9 (3.3)
Discontinuation, no. (%)	15 (5.6)	9 (3.3)	23 (8.5)	18 (6.6)
Due to AEs	2 (0.7)	2 (0.7)	2 (0.7)	4 (1.5)

UTI, Retention more common among elderly

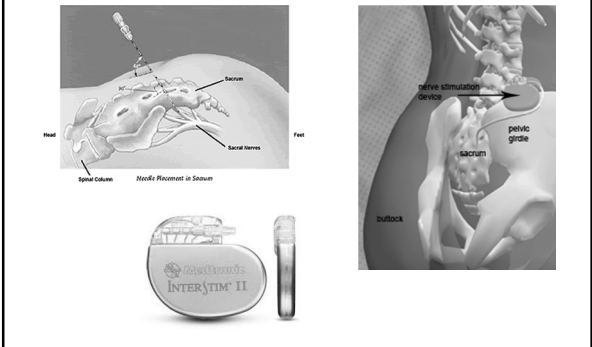
Duration of CIC



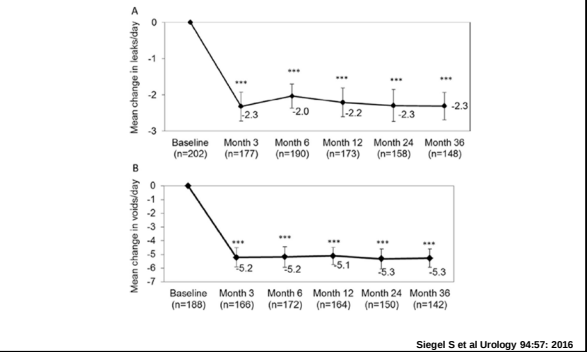
Comparison to medications



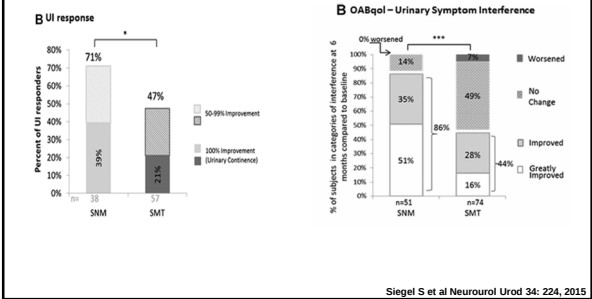
Sacral Neuromodulation Interstim



Multicenter Study of SNM for OAB n=272 patients

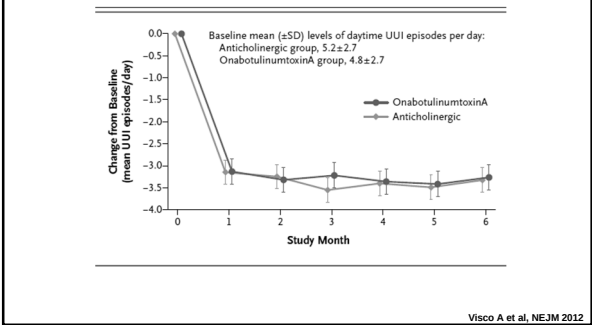


SNM versus Standard Medical Tx n=147 randomized, 6 month data



Important Comparator Trials

ABC Trial – AC vs Botox 100 U

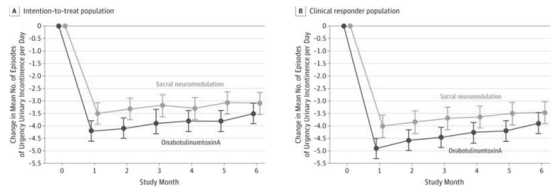


Resolution of incontinence

Table 2. Secondary Outcomes: Efficacy, Quality of Life, and Adverse Events.

Outcome	Anticholinergic Drug	OnabotulinumtoxinA	P Value ^a
Efficacy outcome ^c			
Complete resolution of urgency urinary incontinence — no./total no. (%) ^d	16/119 (13)	30/112 (27)	0.003
Complete resolution of all incontinence — no./total no. (%) ^d	13/119 (11)	26/112 (23)	0.003
>75% reduction in episodes of urgency urinary incontinence — no./total no. (%) ^d	48/119 (40)	61/112 (54)	0.06

Rosetta trial
200 U Botox vs Interstim



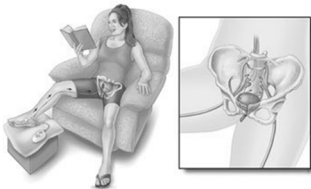
Older age, higher co-morbidity index, increasing BMI associated with poorer outcomes in both arms

Amundsen et al Cont Clin Trials 37: 272, 2014
McCauley JF et al JAMA 317: 535, 2017
Richter HE et al J Urol 198: 890, 2017

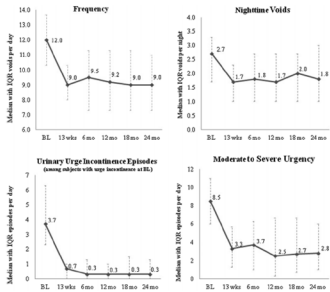
Percutaneous Tibial Nerve Stimulation
Urgent PC



FDA approved Jan 2011
Indication – Refractory OAB
Failed 2 antimuscarinics
12, 30 minute sessions



Long term efficacy - TNS



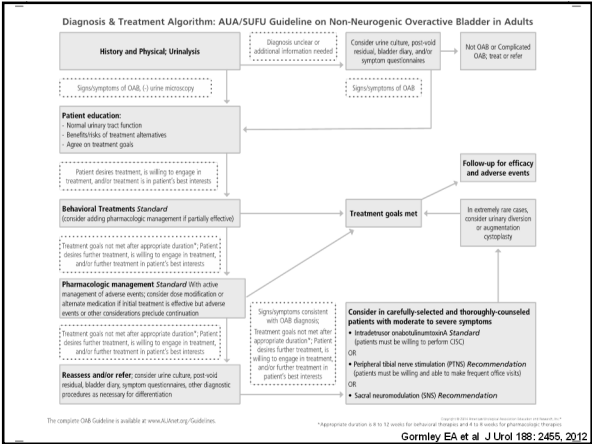
Two treatments over 14 days
Two treatments over 21 days
One treatment over 28 days
Personal treatment plan

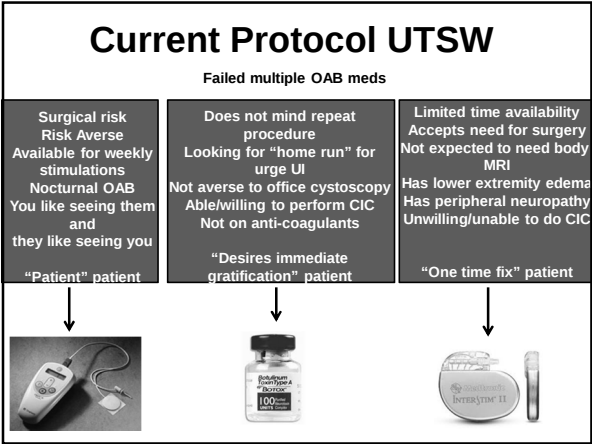
After tapering, mean of 1.3 treatments per month.

Peters KM et al Neurology 32: 24, 2013

Refractory OAB

Augmentation Cystoplasty





Surgical Management of Stress Incontinence in Women

Toby C. Chai, MD
Professor

Department of Urology
Department of Obstetrics, Gynecology & Reproductive Sciences
Yale School of Medicine

Co-Director of Female Pelvic Medicine & Reconstructive Surgery program at
Yale-New Haven Hospital

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Disclosure Statement

- Advisory Role: Avadel

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SLIDE 1

Objectives of Talk

- Evaluation of SUI (Stress Urinary Incontinence) in the index women (no prior SUI surgeries, non-neurogenic, no co-morbidities that might affect bladder function)
- Surgical options for SUI in index women
 - Urethral bulking agent
 - Mesh midurethral sling
 - Autologous fascial sling
- Complications from mesh midurethral slings
- Surgical options for SUI in complex women
 - Prior SUI surgery

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SLIDE 2

What is the International Continence Society (ICS) definition of SUI?

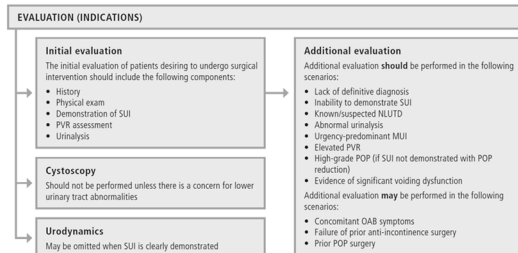
Complaint of involuntary leakage on effort or exertion or on sneezing or coughing

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SLIDE 3

AUA/SUFU Guideline for Female SUI – 2017 Update

Female Stress Urinary Incontinence: AUA/SUFU Evaluation and Treatment Algorithm



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SLIDE 4

Other associated history points that are important – all related to pelvic floor issues

- Lower urinary tract symptoms (frequency, nocturia, hesitancy, straining, etc.)
- Pelvic organ prolapse symptoms and bother (feeling of bulge in vagina, seeing something coming out, feeling of pressure in vagina)
- Fecal motility symptoms and bother (constipation, fecal incontinence)

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SLIDE 5

Decision to treat patient is not based just on having UI symptom

- degree of bother* and impact of UI on patient's *quality of life* (QoL) from the UI

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SLIDE 6

SUI Treatment – AUA/SUFU Guideline Statement

In patients who wish to undergo treatment, physicians should counsel regarding the availability of observation, pelvic floor muscle training, other non-surgical options, and surgical interventions. Physicians should counsel patients on potential complications specific to the treatment options.

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SLIDE 7

SUI Treatment – AUA/SUFU Guideline Statement

TREATMENT

Non-Surgical

- Continence pessary
- Vaginal inserts
- Pelvic floor muscle exercises

Surgical

- Bulking agents
- Midurethral sling (synthetic)
- Autologous fascia pubovaginal sling
- Burch colposuspension

If a midurethral sling surgery is selected, either the retropubic or transobturator midurethral sling may be offered. A single-incision sling may be offered to index patients if they are informed as to the immaturity of evidence regarding their efficacy and safety. Physicians must discuss the specific risks and benefits of mesh as well as alternatives to a mesh sling.

SPECIAL CASES

1. Fixed immobile urethra

- Pubovaginal sling
- Retropubic midurethral sling
- Urethral bulking agents

2. Concomitant surgery for POP repair and SUI

Any incontinence procedure

3. Concomitant NUTD

Surgical treatment following appropriate evaluation and counseling

4. Child-bearing, diabetes, obesity, geriatric

Surgical treatment following appropriate evaluation and counseling

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SLIDE 8

Bulking agents

- Coaptite (calcium hydroxylapatite)
- Macroplastique (Cross-linked polydimethylsiloxane)

A.



B.



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SLIDE 9

Coaptite Outcomes

PMA Clinical Trial, Stamey Grade Improvement

1 year¹ 2 year²

63.4% 66.7%

Coaptite Injectable Implant

1 year¹ 2 year¹

57.0%

Bovine Dermal Collagen

1 n=63 patients out of a total 131 patients who had 12 month follow-up

2 n=26 patients out of a total 39 patients who had 24 month follow-up

3 n=57 patients out of a total 100 patients who had 12 month follow up

4 24 month data not available for Bovine Dermal Collagen patients

Grade 3: Continent (dry)

Grade 3: Urine leakage is associated with vigorous activities such as lifting weights, coughing or sneezing, but never in bed at night.

Grade 2: Urine leakage is associated with activities of minimal stress, such as walking or standing up.

Grade 2: Urine leakage occurs at all times regardless of activity or position.

Table 1

Genitourinary Treatment Related Non-Serious Adverse Events

TYPE OF EVENT	Coaptite® SUBJECTS N=118	
	No. Patients	% Patients
Urinary Retention	65	41.1%
Hematuria	31	19.6%
Dysuria	24	15.2%
UTI	13	8.3%
Urinary Urgency	12	7.6%
Urinary Frequency	11	7.0%
Urgic Incontinence	9	5.1%
Injection Site Pain	3	1.6%
Catheterization Infection	2	1.3%
Erosion	2	1.3%
Urine Analysis Abnormal	2	1.3%
Pelvic Pain	1	0.6%

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SLIDE 10

Macroplastique Outcomes

Ghoniem, G., Corcos, J., Comiter, C., Bernhard, P., Westney, O.L. & Herschorn, S. (2009). Cross-linked polydimethylsiloxane injection for female stress urinary incontinence: Results of a multicenter, randomized, controlled, single-blind study. J Urol. 181, 204-210.

Patient outcomes with Macroplastique¹

At 12 Months

- 62% of patients had an improvement ≥ 1 Stamey Grade²
- 37% of patients were dry²
- Physicians considered 80% of the patients dry or markedly improved^{2a}
- 60% improvement from baseline in Incontinence Quality of Life surveys (IQOL)^{2a}

At 24 Months

- 75% of patients had an improvement ≥ 1 Stamey grade^{2a}
- 33% of patients were dry^{2a}
- No serious treatment-related adverse events associated with Macroplastique

Table 1

Number (%) Subjects Reporting Treatment-Related Adverse Events

Event Category	Macroplastique ¹ (n=122)
Post-procedure catheterization	53 (43.4%)
Urinary tract infection (UTI)	31 (25.4%)
Urinary retention	26 (21.3%)
Dysuria	21 (18.0%)
Hematuria (including transient hematuria)	19 (15.6%)
Pain at implantation site	16 (13.1%)
Frequency ²	14 (11.5%)
Urgency ²	14 (11.5%)
Slowed urine stream	9 (7.4%)
Incomplete bladder emptying	7 (5.7%)
Urgic incontinence	7 (5.7%)
Hesitancy	6 (4.9%)
Vaginal bleeding	4 (3.3%)
Year infection	4 (3.3%)
Bladder pain	3 (2.5%)
Cystitis	3 (2.5%)
Increased/worsening nocturia	3 (2.5%)
Obstructive bladder (OAB)	3 (2.5%)

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SLIDE 11

473

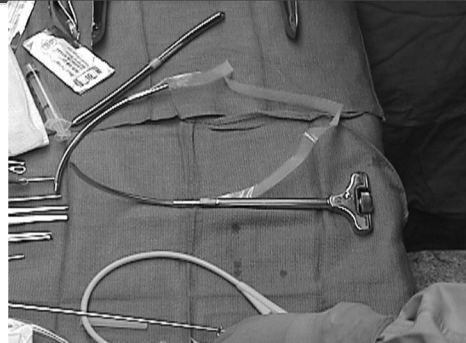
Mid-Urethral Polypropylene Slings

- Retropubic (e.g. TVT)
 - up->down
 - down->up
- Transobturator
 - Inside->out (TVT-O)
 - Outside->in (MONARCH)

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SLIDE 12

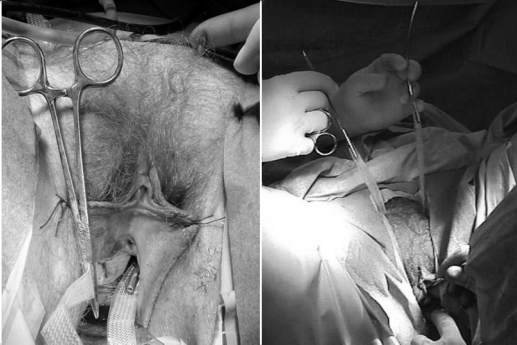
Retropubic (down->up) midurethral polypropylene sling (TVT®)



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SLIDE 13

Placement of the retropubic midurethral mesh (TVT®)



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SLIDE 14

Placement of transobturator sling (outside -> in) (MONARCH)



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SLIDE 15

Placement of transobturator sling (outside -> in) (MONARCH)



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SLIDE 16

Placement of transobturator sling (outside -> in) (MONARCH)



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SLIDE 17

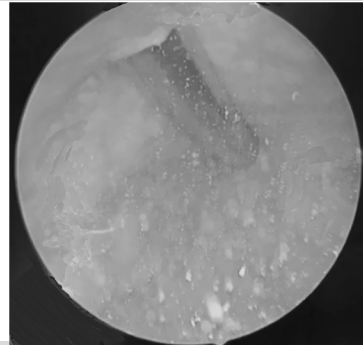
Complications of midurethral slings

- Bladder perforation
- Injury to major blood vessels, bowel during trocar pass intraop (retropubic approach)
- Recurrent urinary tract infections
- Urinary retention
- De novo overactive bladder symptoms
- Pelvic pain / thigh pain / dyspareunia
- Erosion of mesh into vagina, bladder, urethra, bowel in the post-operative period at any time

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SLIDE 18

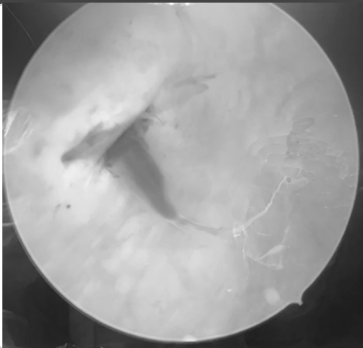
Retropubic mesh sling (TVT®) with trocar puncture of the patient's bladder on right side



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SLIDE 19

Trocar is RE-PASSED, trocar left in, cystoscopy no perforation is seen



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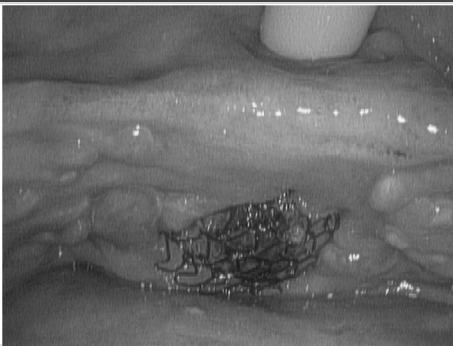
SLIDE 20

Series of Erosion Pictures

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SLIDE 21

Vaginal erosion of polypropylene mesh



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SLIDE 22

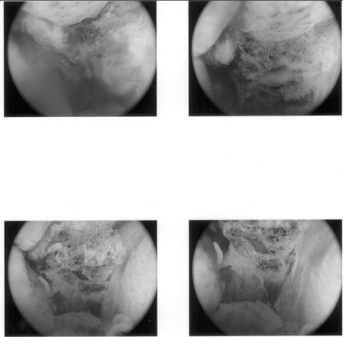
Vaginal erosion of polypropylene mesh



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SLIDE 23

Vaginal erosion of polypropylene mesh



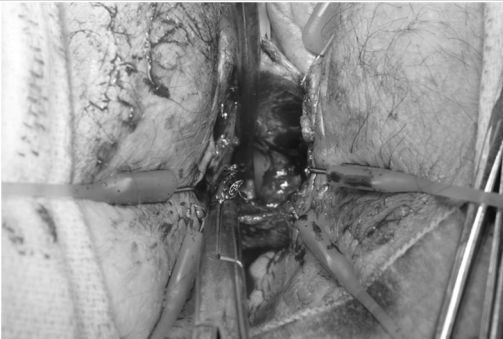
Yale SCHOOL OF MEDICINE SLIDE 24

Vaginal erosion of polypropylene mesh



Yale SCHOOL OF MEDICINE SLIDE 25

Urethral erosion of mesh



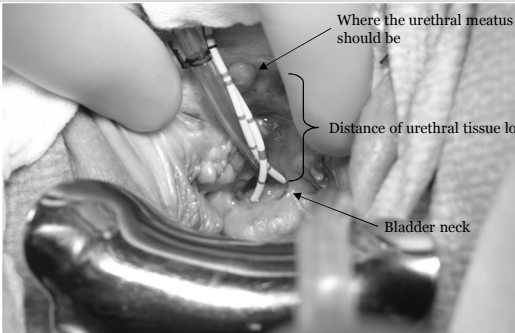
Yale SCHOOL OF MEDICINE SLIDE 26

Complete urethral loss
(after vaginal portion of mesh removed)



Yale SCHOOL OF MEDICINE SLIDE 27

Complete urethral loss from mesh erosion into urethra
(after vaginal portion of mesh removed)



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Editorial about 2 papers published in Sept 2017
Journal of Urology about mesh removal

Mesh Sling Removals: Why, When, How and Consequences

Several treatments for pelvic organ prolapse (POP) and stress urinary incontinence (SUI) using transvaginal mesh kits have provided durable, continent, strong, and safe outcomes. While the use of transvaginal mesh for POP reconstruction has waned considerably, using mesh slings via the mid-urethral retropubic and mid-urethral trans-obturator approaches for SUI remains popular. AUA (American Urological Association) and SUI (Society of Urology, Female Pelvic Medicine and Urogynecological Society) issued a joint position statement in January 2014 supporting mid-urethral mesh slings as the gold standard for surgical treatment of SUI. A Cochrane Database review also highlighted the efficacy and safety of mesh slings.¹

underwent a repeat mesh or autologous sling procedure while 50% were treated with urethral bulking injections and 50% received pelvic floor physical therapy.

Boe et al (page 498) analyzed postoperative complications of transvaginal mesh removal within 90 days in 277 patients between 2007 and 2015 using the Clavien-Dindo classification.² This population was not as homogeneous as in the prior study¹ because removal of mesh placed for stress incontinence and pelvic organ prolapse was included. The mesh removal included sling mesh in 40% of cases, POP mesh in 13%, and sling and POP meshes in 32%. The indicators for mesh removal were bladder neck obstruction and/or urinary retention in 52% of cases, vaginal extrusion in 33%, lower urinary tract symptoms in 10% and erosion into the

reports, slings were removed 2 to 8 years after implantation.^{3,4} Therefore, long-term follow-up of patients who receive mesh slings is pertinent and probably should be indicated. Some 60-year-olds incocontinent developed between 30% and 35% of the time, this means that it is more likely that a woman will receive stress incontinence than become incontinent after mesh sling removal. This is something that we can tell our patients who are facing mesh sling removal.

Although the complications of partial mesh sling removal are common, they are relatively minor.

Since we do not know the denominator (the total number of those who received a mesh sling) from which these 2 study cohorts were drawn,⁵ we cannot infer the actual mesh sling complication rate.

Talley C Choi
Departments of Urology and Obstetrics, Gynecology and Reproductive Sciences
Yale University School of Medicine
New Haven, Connecticut

J Urol. 2017 Sep;198(3):496-497.

Yale SCHOOL OF MEDICINE SLIDE 29

My editorial about 2 papers published in Sept 2017 *Journal of Urology* about mesh removal

What are the takeaway messages from these papers? Although mesh slings are considered the gold standard procedure, complications requiring removal still develop. As presented in these 2 reports, slings were removed 3 to 6 years after implantation.^{5,4} Therefore, long-term followup of patients who receive mesh slings is paramount and probably should be indefinite. Since de novo stress incontinence developed between 10% and 20% of the time, this means that it is more likely that a woman will remain stress continent than become stress incontinent after mesh sling removal. This is something that we can tell our patients who are facing mesh sling removal.

Although the complications of retropubic mesh sling

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SLIDE 30

Which midurethral sling is better – retropubic or transobturator?

- Some data suggest retropubic is better than transobturator, especially for low VLPP (Valsalva leak point pressure) and low MUCP (maximum urethral closure pressure) situations
- Risks for retropubic versus transobturator slightly different (increased bladder and bowel perforation risk with retropubic, increased thigh/leg pain risk with transobturator)

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SLIDE 31

TOMUS Trial: TVT versus TVT-O/MONARCH RCT n~600 (~300 TVT and ~300 TVT-O)

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Retropubic versus Transobturator Midurethral Slings for Stress Incontinence

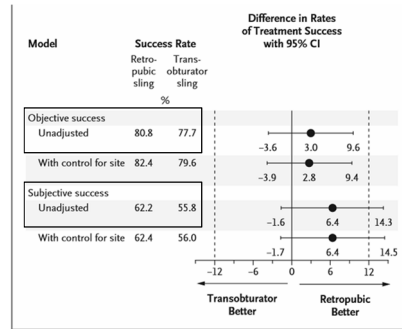
Holly E. Richter, Ph.D., M.D., Michael E. Albo, M.D., Halina M. Zyczynski, M.D., Kimberly Kerton, M.D., Peggy A. Norton, M.D., Larry T. Siris, M.D., Stephen R. Kraus, M.D., Toby C. Chai, M.D., Gary E. Lemack, M.D., Kimberly J. Dandreo, M.Sc., R. Edward Varner, M.D., Shawn Meneffee, M.D., Chiara Ghetti, M.D., Linda Brubaker, M.D., Ingrid Nygaard, M.D., Sali Khandwala, M.D., Thomas A. Rozanski, M.D., Harry Johnson, M.D., Joseph Schaffer, M.D., Anne M. Stoddard, Sc.D., Robert L. Holley, M.D., Charles W. Nager, M.D., Pamela Mosall, M.D., Ph.D., Elizabeth Mueller, M.D., Amy M. Arisco, M.D., Marlene Corton, M.D., Sharon Tennstedt, Ph.D., T. Debuene Chang, M.D., E. Ann Gormley, M.D., and Heather J. Litman, Ph.D., for the Urinary Incontinence Treatment Network*

N Engl J Med. 2010 Jun 3;362(22):2066-76.

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SLIDE 35

Trial Design was a EQUIVALENCE trial with 12 months post-op as primary outcome timepoint



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SLIDE 35

Composite Outcome Assessment

- Objective criteria for success
 - Negative cough stress test
 - Negative 24-hour pad test
 - No retreatment for SUI (behavioral, pharmacologic or surgical treatment for SUI)
- Subjective criteria for success
 - Absence of self-reported symptoms of SUI using validated PRO instrument
 - No leakage recorded on a 3-day voiding diary
 - No retreatment fro SUI

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SLIDE 34

TOMUS Trial: 24 months data

Treatment Success of Retropubic and Transobturator Mid Urethral Slings at 24 Months

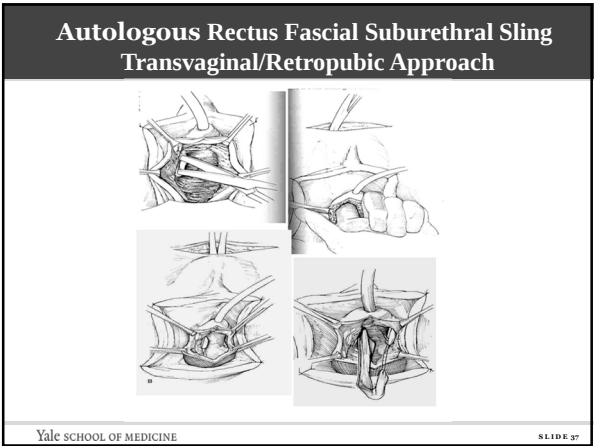
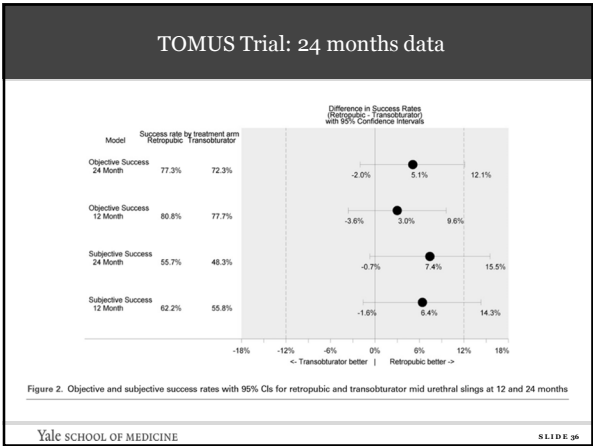
Michael E. Albo,*†, Heather J. Litman,‡, Holly E. Richter,§ Gary E. Lemack,|| Larry T. Siris,‡ Toby C. Chai,¶ Peggy Norton,‡ Stephen R. Kraus,** Halina Zyczynski,†† Kimberly Kerton,‡ E. Ann Gormley†† and John W. Kusek† for the Urinary Incontinence Treatment Network

From the University of California, San Diego, La Jolla, California (MEA), New England Research Institutes, Watertown, Massachusetts (HJL), University of Alabama at Birmingham, Birmingham, Alabama (HJR), University of Texas, Southwestern, Dallas (GEL), and University of Texas at San Antonio, San Antonio (SRL), Texas, William Beaumont Hospital, Royal Oak, Michigan (LTS), University of Maryland, Baltimore (TCC), and National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda (JWK), Maryland, University of Utah, Salt Lake City, Utah (PH), University of Pittsburgh, Magee-Womens Hospital, Pittsburgh, Pennsylvania (HJ), Loyola University Chicago, Chicago, Illinois (KK), and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire (JAG)

Journal of Urology 2012 Dec;188(6):2281-7.

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SLIDE 35



Up to a 30 cm long fascial lata strip can be obtained



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SLIDE 42

What do we do next when a patient fails a mesh sling?

First, let's define what might comprise "failure"

- Urinary retention
- Recurrent UTI
- Altered patterns of voiding (bending, straining, hesitancy)
- De novo overactive bladder symptoms / urgency urinary incontinence
- Recurrent stress urinary incontinence
- Mixed urinary incontinence
- Dyspareunia

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SLIDE 43

Sling complication considerations

- If bothersome symptoms such as urinary retention, incomplete bladder emptying, difficult voiding, straining/hesitancy to void occur immediately after sling surgery, cut sling without any other tests
- De novo OAB symptoms may represent idiopathic cause or response to bladder outlet obstruction. Consider doing urodynamics for de novo OAB to help clarify whether bladder outlet obstruction is present in which case, cutting sling may resolve OAB symptoms.
- Recurrent UTI can be a harbinger to erosion of sling into urinary tract (bladder, urethra) and formation of stone on . Patient may also have outlet obstruction as cause for recurrent UTI.

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SLIDE 44

What happens to bladder outlet after a sling?
urodynamics pre- and post- sling

Female Urology

Urodynamic Changes Associated with Successful Stress Urinary Incontinence Surgery: Is a Little Tension a Good Thing?

Stephen R. Kraus, Gary E. Lemack, Larry T. Siris, Toby C. Chai, Linda Brubaker, Michael Albo, Wendy W. Leng, L. Keith Lloyd, Peggy Norton, and Heather J. Litman, for the Urinary Incontinence Treatment Network*

Urology. 2011 Dec;78(6):1257-62.

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SLIDE 45

CHANGE in UDS for autologous slings –
Post minus Pre Values

	Success		Failure		P Values
	n	Mean (SD)	n	Mean (SD)	
NIF Q _{max}	84	-5.0 (12.5)	93	-3.8 (13.8)	.52
NIF volume	84	13.0 (192.4)	93	-33.5 (157.8)	.58
NIF PVR	84	11.1 (61.65)	93	8.0 (56.3)	.26
MCC	96	4.5 (130.14)	103	-42.1 (152.4)	.29
Compliance	71	5.8 (241.4)	79	-37.52 (230.5)	.09
PFS Q _{max}	36	-3.0 (9.2)	48	-4.6 (8.8)	.79
Pdet@Qmax	36	18.1 (20.9)	47	6.0 (13.5)	.008
BOOI	36	24.2 (29.5)	47	14.8 (24.0)	.09

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SLIDE 46

What to do next after patient fails a sling with recurrent SUI?

Clin Urol Rep (2014) 15:427
DOI 10.1007/s11934-014-0427-0

FEMALE UROLOGY (K KOBASHI, SECTION EDITOR)

Management of Recurrent Stress Incontinence Following a Sling

Genevieve Nadeau - Sender Herschorn

- Tightening of implanted sling
- Repeat midurethral sling
- Bladder neck sling
- Autologous fascial sling (rectus fascia, fascia lata)
- Spiral sling
- Re-adjustable sling (Remeex®)
- Adjustable continence therapy
- Artificial urinary sphincter
- Urinary diversion

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SLIDE 47

Conclusions

- Surgical approaches can be used effectively to ameliorate SUI
- However, selection of patients is important. Properly selected and counseled patients will have the best outcomes
- **Shared decision making** is a key component of patient- centered health care. It is a process in which clinicians and patients work together to make **decisions** and select tests, treatments and care plans based on clinical evidence that balances risks and expected outcomes with patient preferences and values

MANAGEMENT OF SPHINCTERIC URINARY INCONTINENCE IN MEN AFTER RADICAL PROSTATECTOMY

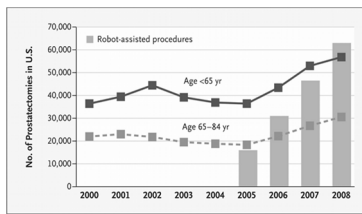
Craig V. Comiter, MD

Professor, Urology
Stanford University Medical School

DISCLOSURE STATEMENT

- Nothing to disclose

PPI IS BECOMING MORE COMMON... BECAUSE OF THE ROBOT



And the rate of PPI remains steady at approximately 10% , and up to 30% in older men

- 200,000 cases of prostate cancer per year in US
 - 40% will choose RRP for treatment
- Not all men who leak will elect further treatment
 - 6%-9% with enough bother for surgery for PPI
 - Stanford JL, JAMA 2000; 283:354-360.
 - Litwin MS, J Urol 2000; 164:1973-1977.
 - Kuntz SO, J Urol 2004; 172:2267-2281.
 - 2-5% (American - Canadian) will opt for surgery

RISK FACTORS

- Pre-operative continence status
 - And voiding dysfunction
- Tumor stage
- Age at time of surgery
- Functional urethral length
- Previous XRT
- Obesity

PRE-OP INCONTINENCE

- US adults – 5.4% with incontinence
 - 26% of those with isolated SUI (1.3% background SUI)
 - Highest risk for PPI
 - Baseline ISD
- Pre-op bladder dysfunction adversely affects post-op continence
 - Neurogenic DO
 - Pre-op BPO
 - DO, DUA, myogenic insult

STAGE / SURGICAL APPROACH

- Poor correlation between stage and incontinence
 - But stage may affect approach – Loeb S, Urology, 2007; 69:1170-1175.
- Nerve sparing
 - No difference (Lepor H, J Urol 2004; 171:1216)
 - Beneficial effect of bilateral nerve sparing (Handgash KC, Urology, 2007; 70:1127)
- Bladder neck preservation
 - Improved continence at 3 months, no change by 6-12 months
 - (Srougi M, Urol 2001; 155:815-818).
- Robot/Lap vs Open RP
 - Similar outcomes (Aberling TE, Urology 2004; 63:819)
- Perineal vs RP – no difference (Young MD, J Urol 2003; 170:2374)

AGE

- Advanced age as a risk factor
 - Rogers CG, J Urol 2006; 176:2448-2452.
- vs delay in return to continence
 - Lepor H, J Urol 2004; 171:1216-1219.
- Men age 70-74 3x more likely to undergo AUS for PPI compared to those age 45-49
 - Rogers CG, J Urol 2006; 176:2448-2452.
- Progressive reduction in sphincter striated muscle cells with age
 - Young MD, J Urol 2003; 170:2374-2378.

PRE-OP FUNCTIONAL URETHRAL LENGTH

- Pre-op length of functional/membranous urethra
 - related to PPI
- MRI
 - If length > 12 mm, 89% continence
 - If length < 12 mm, 77% continence
- UDS
 - Shorter functional urethral length predicts incontinence
 - Strasser H, J Urol 1998; 159:100-104.
 - Van Kampen M, Urol Int 1998; 60:80-84.

OBESITY

- BMI > 30 kg/m²
 - Higher risk of post-op complications
 - Wound infections, anastomotic stricture, urinary incontinence
 - Up to 3x risk of incontinence for obese vs non-obese
 - 25% of men with BMI > 30 kg/m² with PPI Difficulty with urethral anastomosis, adverse medical factors
 - DM, vascular disease, HTN
- Wolin KY, J Urol 2010; 183:629-633.

XRT

- Salvage RP (after XRT)
 - Effective option in carefully selected patients
 - Increased risk of complications
 - Rectal injury, anastomotic stricture, PPI
 - PPI in 25%-78%
 - Nearly 50% AUS rate after salvage RP
- Sanderson KM, J Urol 2006;176:2025-2031.

PATHOPHYSIOLOGY

- Bladder vs Outlet
 - Bladder
 - DO, DUA, poor compliance
 - Outlet
 - ISD, BOO, ? Mobility
 - Stricture, BOO – overflow
- Consider pre-operative bladder dysfunction

BLADDER DYSFUNCTION

- Pre-existing vs de novo
 - Denervation, obstruction
- Post –op impaired contractility, poor compliance
 - Previously thought to resolve by 8 months
 - Recent: ↓ compliance in 1/3, persists in 28% at 36 mos
 - Detrusor underactivity in 1/2, persists in 25% at 36 mos
 - Giannantonio A, J Urol 2004;171:1569-1566.
 - Giannantonio A, Eur Urol 2008; 54:657-664.
- Persistent bladder dysfunction in significant minority even up to 3 years post-op

EVALUATION

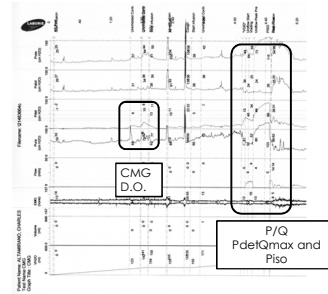
- History
 - Pre-op continence, defecation
 - Pharmacotherapy, other therapy
 - XRT, TURP
- Physical exam
 - GU tract, neuro-urological
 - S2-S4 segments – perineal sensation, PF contraction, BCR, DRE
- Urinalysis, PVR
- Freq, nocturia, incontinence episodes, voided volume, 24-hr output
 - Fluid intake, bladder capacity, freq of leakage
 - 4-day diary = to 7 day diary
 - Fosters compliance
- 24-hr home-based pad test
 - More reproducible than 1-hour test
 - 24 hr pad test easier to perform, can be standardized,
 - 1 hour test has its own advantages: no need for home test and water tight container
 - Schick E, Neuro Urol Urolyn 2003; 22:92-96.
 - Mourtisen L, Neuro Urol Urolyn 1989;8:579-587.

INDICATIONS FOR URODYNAMICS

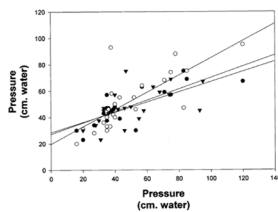
• Ask a question whose answer affects treatment algorithm or outcome

- Example: is there storage dysfunction? Bladder dysfunction?
- Post-op impaired contractility, poor compliance
- Is there SUI due to ISD? Or DO?
 - Or both?
- Is there BOO?
 - Could be answered with cystoscopy if there is a tight stricture
- Can the bladder contract adequately –
 - To permit emptying after sling placement?
- If there is no question, then UDS is not indicated
 - Or if the answer does not affect the outcome

UDS FOR PPI



LPP



MUCP, ALPP and RLPP are highly correlated in men with PPI and can be used interchangeably in men with PPI

FIGURE 2. Correlation among leak point pressures. Filled circle, ALPP vs. RLPP ($r = 0.79$, $P < 0.001$); open circle, ALPP vs. MUCP ($r = 0.75$, $P < 0.0001$); triangle, MUCP vs. RLPP ($r = 0.59$, $P < 0.005$).

Comiter CV et al. Urol 2003 62: 75-78

UDS – THE PUNCH-LINE

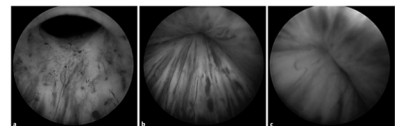
- ISD as sole cause in $> 2/3$
- Isolated bladder dysfunction $< 10\%$
- Sphincter and bladder dysfunction coexist in $1/3$
 - Groutz A, J Urol 2000;163:1767-1770.
 - Ficazzola MA, J Urol 1998;160:1317-1320.

CHARACTERIZATION OF SUI CAN AFFECT DECISION

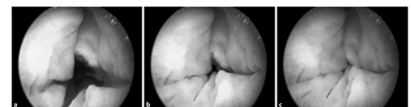
- Urethral mobility affects T-O sling outcome
 - Repositioning test
 - Rehder P, Arch Esp Urol 62:860, 2009
 - Residual sphincter function affects sling outcome
 - Soljanik I, World J Urol 30:201, 2012
- LPP
 - Success of urethral bulking higher in those with higher LPP
 - < 60 cm water predicts failure
 - Sanchez-Ortiz RF, J Urol 158:2132, 1997
- Degree of urethral mobility varies in different patients
 - Comiter CV, et al, WSAUA, 2010

OPTIMIZING PT SELECTION - REPOSITIONING TEST

- Positive - (adequate coaptation)



With elevation of the perineum by the examiner during urethroscopy, there is contraction of the EUS



- Negative (poor coaptation)

OPTIMIZING SLING RESULTS- SELECTING IDEAL PATIENT BASED UPON URODYNAMICS

- Rule out obstruction
 - BOO due to anastomatic stricture in 2.7%-20%
 - Kundu SD, J Urol 2004; 172:2227-2231.
 - Kao TC, J Urol 2000; 163:858-864.
- Assess for DO
 - D.O., low capacity adversely affects sling outcome
 - Warner JN, Neurosurg Urology 2012; 31:1124-7
 - Crites MA, Urology 2011; 7:63.
- Check contractility
 - Detrusor Underactivity (DUA) relative contraindication to sling
 - Potentially obstructive sling in pt with DUA poses risk of retention
 - Sling is designed to prevent leakage with straining
 - Therefore interferes with/prevents voiding by Valsalva
 - In large cohort of men with PPI, no instances of prolonged retention in men with normal contractility
 - Comiter CV, Neurosurg Urology 2005; 24:648-653.
- Versus rates of 2% to 21% in cohorts without UDS

DEFINING OUTCOME- DEFINING CONTINENCE

- Can only optimize if we can define/measure success
- Defining continence after RRP – in the literature
 - Total control/perfect continence/dry
 - Occasional leakage, no pad
 - < 1 pad per day
 - 1/3 to 1/2 of men who do not wear pads will have occasional leakage of urine
 - Wallerstedt A, et al. J Urol 187 196, 2012
 - Rodriguez E et al, Urology 67: 785, 2006.
- HRQOL strongly correlates with level of leakage
 - Wearing 1 pad (even if 'security' pad)
 - Negatively affects QOL vs wearing no pad at all
 - Liss MA, et al: J Urol 183:1464, 2010

SHOULD WE USE SIMILAR OUTCOME MEASURES AFTER SURGERY?

- Men are generally dry before RRP
 - Thus wearing a pad after is a major deterioration
 - Very rarely are LUTS improved with RRP
- Men are always wet before PPI surgery
 - Improvement is likely
 - Worsening is unlikely
 - Pad free or dry may be difficult (and unnecessary)
 - HRQOL has **not** been shown to differ in men with and without 1 pad per day use following SUI surgery
- Set reasonable expectations –
 - Pad free during non strenuous activities
 - Need pad during straining

WHAT OUTCOMES MEASURES ARE APPLICABLE AFTER PPI SURGERY?

- Subjective
 - **Patient Global Impression of Improvement (PGI-I)**
 - **Preferred subjective measure of success**
 - Worse, same, better, much better, very much better
 - Much better & very much better = success
 - FDA, SUFU
- Objective
 - Pad weight
 - 24 hour pad test
 - 1 hour pad test (ICS)
 - Pad use
- What is cure vs success vs failure?

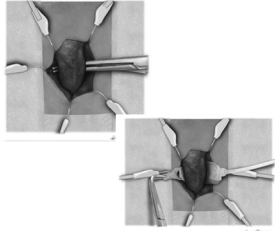
DEFINING SUCCESS – ACCORDING TO THE FDA (AT 12 MONTHS)

- Objective: change in 24-hour pad weight
 - **Cured: Dry, < 1.3 g on 24 hour pad test**
 - **Very Much Improved: <12 gm or 90% reduction in pad weight**
 - **Much Improved: 50% - 89% reduction of pad weight**
 - Improved: 25% - 49% reduction of pad weight
 - Failed: < 25% reduction of pad weight
- Subjective: PGI-I score post implant
 - **Very much better**
 - **Much better**
- Secondary endpoints:
 - ICIQ and UCLA-RAND Incontinence Index
 - Change in pad use
 - Device and procedure related adverse events

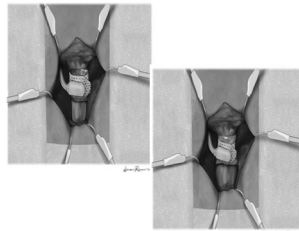


AUS

CIRCUMFERENTIAL DISSECTION



CIRCUMFERENTIAL COMPRESSION



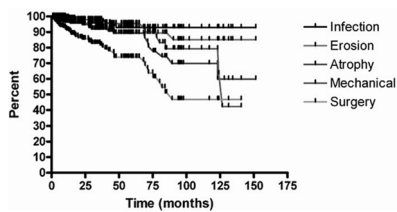
AUS advantages

- Predictable success
 - Regardless of degree of SUI
- Best choice for XRT
- Best choice for revision surgery
- Long term data
- Minimal postoperative pain
- Detrusor overactivity
 - No adverse effect on outcome
 - Lai HH et al. Urol 2009, 73: 1264-1269
- Poor detrusor contractility
 - No adverse effect on outcome
 - Lai HH et al. Urol 2009, 73: 1264-1269

AUS disadvantages

- Pt need to manipulate pump
- Erosion rate
- Infection rate
- Revision rate
 - 21% at 5 years
 - 50% at 10 years
- Worry about catheterization

RATE OF AUS FAILURE



At 5 years – 25% of the cohort had undergone revision surgery / removal
At 7.5 years – 50% of the cohort had undergone revision surgery / removal

Lai HH et al. J Urol 2007 177: 1021-1025

EARLY FAILURE

- Early (persistent incontinence)
 - Cuff is too large/loose
 - Improper reservoir pressure
 - Device puncture / fluid leak
 - Detrusor overactivity
 - Poor compliance
 - Urinary retention

Ideally use a 4.0 to 4.5 cm cuff
61 – 70 cm H₂O reservoir

LATE FAILURE

- Device malfunction
- Urethral Atrophy
- Urethral Erosion
- Detrusor Overactivity
- Decreased Bladder Compliance
- Inadvertent Device Inactivation

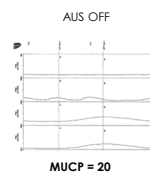
IMAGING

- Radiograph (if contrast used)
 - Determine reservoir and pump filling
 - Do both open and closed
 - Theoretic risk of crystals with contrast if mixed improperly
- Ultrasound
 - Examine for fluid in reservoir
- IF MISSING FLUID THIS SUGGESTS A LEAK
 - However only 2cc of leak can lead to malfunction (HARD TO SEE)

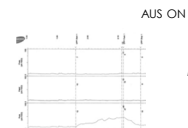
UPP (CUFF ATROPHY)

- A pressure differential of 40cm H₂O or less suggests sphincter malfunction

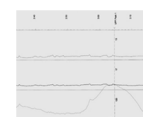
- My thought.....
 - If LPP/MUCP less than 60cm H₂O then a problem



MUCP = 20



MUCP = 35



MUCP = 120

URETHRAL EROSION

- Remove all hardware
- Attempt to repair urethra / capsule
- 16 F catheter for 3-4 weeks (16 F)
- Redo surgery 6-24 weeks later
 - Cystoscopy first to rule out stricture
 - New site
 - Transcorporal ?



URETHRAL ATROPHY

- New site
- Transcorporal placement
- Downsize cuff
 - 3.5 cm cuff now available
 - No increased risk of erosion compared to larger cuff ¹
- Double cuff
 - Usually second more proximal
 - Need to increase fluid in reservoir by 2 or 3 cc's
 - Increased risk of complication compared to single cuff ²
- Urethral wrap
 - One small case series – 5 of 8 patients failed ³
- Increased reservoir pressure

1) Hudak SJ et al. J Urol 2011, 186: 1962-1966 2) O'Connor RC et al. Urol 2008, 71: 90-93
3) Trost L et al. Urol 2011, in press

The good news is...

- 1 ppd rates 59-90%
 - Perez, Webster, J Urol, 1992
 - Gomha, Boone, J Urol, 2002
- Pad free 10-72%
 - Martins, Boyd, J Urol, 1995
 - Litwiler, et al, J Urol, 1996
- Satisfaction rates 87-90%
 - Haab, et al: J Urol, 1997
 - Lai, et al: J Urol, 2007
 - Elliott Barrett, J Urol, 1998
- AUS most predictably successful surgery for PPI
- Largest body of literature with long term success

The bad news is...

- Explantation 7-17%
 - Gousse, et al: J Urol, 2001
- Mechanical Failure + Urethral atrophy 8-45%
 - Lai, et al, J Urol, 2007

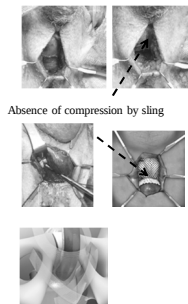
SLING – MECHANISM OF ACTION

The principle of continence/urethral support is similar for all slings

- elevation and suspension of the pelvic floor muscles
- passive compression of the urethra
- Sustained sling tension is necessary for continence
 - Over-correction with consequent urinary retention
 - Under-correction with recurrent incontinence
- Balance of continence, adequate emptying, patient satisfaction.

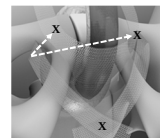
THE EVOLUTION OF THE SLING – NON ADJUSTABLE

- Transobturator Retroluminal Sling
 - Relocates proximal urethra – non compressive
 - Has minimized surgical invasiveness
- Perineal Bone Anchored Sling
 - Compresses perineal urethra
 - Excellent fixation with bone anchors
- Quadratic Sling
 - Relocate proximal urethra **and** compress perineal urethra



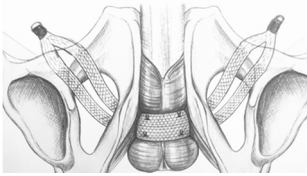
QUADRATIC SLING - VIRTUE

- 5.5 x 7 cm large pore monofilament polypropylene mesh
 - Inferior (trans-obturator, TO) extensions - 1.5x 22.5 cm
 - Superior (pre-pubic, PP) extensions - 1.5 x 25 cm
- T-O component relocates proximal urethra
- P-P component broadly compresses perineal urethra
 - Avoids bone anchors
 - Slippage of sling off bulbar urethra not possible
 - Due to pre-pubic component
- Further evolution to "Fixation"
 - Improved subjective (PGI-I) and objective (pad weight) results
 - Prevents early loss of efficacy



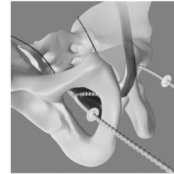
I-STOP TOMS

- Outside-in trocar passage
- Sling arms withdrawn on either side
- Pulled firmly and sutured to bulbospongiosus
- Perineal body not dissected



Grise, Urology, 2012

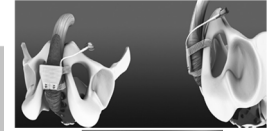
ADJUSTABLE SLINGS- ALTERNATIVE FOR RECURRENT LEAKAGE



ARGUS



REMEEX



ATOMS

BONE-ANCHORED SLING RESULTS – 24 MOS. MEAN F/U – AUTHOR-DEFINED SUCCESS

Study	# pts	Mean fu (months)	Sling material	Cure (%)	Cure/Improve (%)	Fail (%)
Ulinich 2004	36	25	Synthetic	67	92	8
Stern 2005	75	48	Synthetic	36	68	32
Rajpurkar 2005	46	24	Synthetic or organic	37	74	26
Conlter 2005	48	48	Synthetic	65	85	15
Migliari 2006	49	32	Synthetic	30	63	37
Fischer 2007	62	56	Synthetic	37	58	42
Gilberti 2008	36	41	Synthetic or organic	62	70	30
Guimaraes 2009	62	28	Synthetic	65	88	12
Carmel (2009)	45	36	Synthetic	36	76	24
Athanasopoulos (2010)	43	24	Synthetic	51	81	19

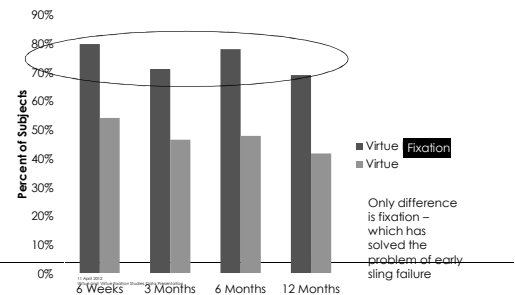
TRANSOBTURATOR SLING RESULTS – AUTHOR DEFINED

Study	N	Mean fu (months)	Cure (%)	Cure/Improve (%)	Fail (%)
Rehder (2010)	118	12	74	91	9
Grise (2011)	122	12	59	87	13
Bauer (2011)	126	27	52	75	25
Cornel (2010)	35	12	9	54	46
Cornu (2011)	136	21	62	78	22
Chaparro (2009)	20	24	65	65	35
Li (2012)	66	24	32	56	44
Grise (2012)	103	12	59	79	21
Rehder (2012)	156	36	42	77	23
Collado (2013)	61	26		80	20

ADJUSTABLE SLING RESULTS – AUTHOR DEFINED

Study	# patients	Mean fu (months)	Type of Adjustor	Cure (%)	Cure/Improve (%)	Fail (%)
Moreno-Sierra 2006	48	7.5	Argus	73	83	17
Romano 2006	51	32	Argus	65	85	15
Romano 2009	47	45	Argus	66	79	21
Hubner 2011	101	27	Argus	79	79	21
Bochavave-Overglouw 2011	100	27	Argus	40	72	28
Dolpiaz 2011	29	35	Argus	17	28	72
Sousa-Escandon 2007	6	18	REMEEX	83	100	0
Jimenez 2010	14	19	REMEEX	42	75	25
Hoda 2013	99	18	ATOMS	63	92	8

VIRTUE MALE SLING RESULTS – PGI-I MUCH AND VERY MUCH BETTER



RISK FACTORS FOR SLING FAILURE

- Historical Risks
 - Prior AUS
 - XRT
 - Prior urethral stricture
- Degree of Incontinence
 - Higher pad weight
 - > 200 g/24 hrs
 - > 450 g/24 hrs
 - Higher pad use
- Urodynamic Risks
 - Low MUCP
 - Low ALPP
 - Low functional urethral length
 - **Presence of DO**
- Repositioning Test
 - **Weak residual sphincter function**
 - Incomplete closure of sphincter
- Surgical Technique
 - **Failure to tunnel sling**
 - **Poor sling/suture fixation**
 - Surgeon inexperience
 - Non-familiarity with new technique

•Comu JN, et al: 8 JUL 2010;108:236
 •Soljanik I : World J Urol 2012 30:201
 •Criles MA, et al: Urology 2011
 •Fisher MC, J Urol 2007
 •Comiter, Curr Opin Urol, 2007, 2015

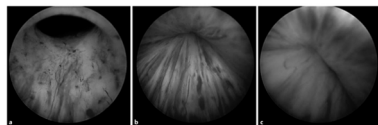
MAIN RISK FACTOR FOR FAILURE...

- Most of the aforementioned factors equate with worse ISD
 - History: severe leakage
 - XRT, brachytherapy, cryotherapy
 - Pad test: high volume
 - UDS: low MUCP, LPP
 - Negative repositioning test
- With suboptimal urethral compression

OPTIMIZING PT SELECTION - URETHRAL REPOSITIONING TEST



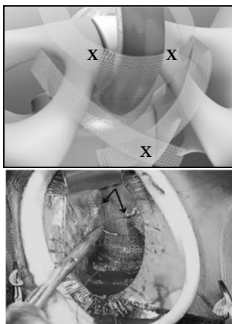
With elevation of the perineum by the examiner during urethroscopy, and by sling tensioning, there is contraction of the EUS



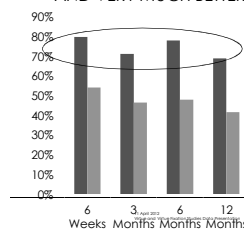
OPTIMIZING RESULTS – REPOSITIONING TEST - PROGNOSIS

- Positive test: sphincter closes concentrically during repositioning
 - Lengthening of zone of coaptation by > 1 cm
- Positive in 81.5%
 - 83% cure/no pads
- Negative in 18.5%
 - 25% cure/no pads
- Correlates to Marshall test in women
- Urethral mobility affects T-O sling outcome

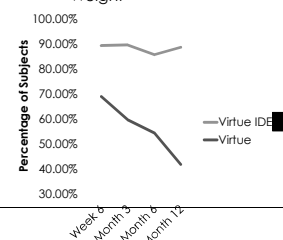
SLING FIXATION IS VITAL



VIRTUE MALE SLING RESULTS – PG-I MUCH AND VERY MUCH BETTER

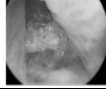


Median % Reduction in Pad Weight



EVALUATION OF PERSISTENT PPI FOLLOWING SLING

- History and Physical Exam
 - Did original sling work temporarily?
 - Timing of recurrent incontinence
 - Stress vs urge
 - Demonstrate leakage during strain
- Urodynamics
 - Only if there is a questions whose answer changes treatment
 - Bladder vs outlet leakage
 - Contractility
 - If considering a more compressive/quadratic or adjustable sling
 - Uroflow/PVR can rule out obstruction/incomplete emptying
- Cystoscopy
 - If stricture is suspected
 - If erosion is suspected



1. Harris et al Urology, 2008 (E pub)

TREATMENT OPTIONS FOR RECURRENT INCONTINENCE AFTER SLING

- Periurethral bulking injection
- Place second transobturator sling
 - Remove sling
 - Leave sling *in situ*
- Place quadratic sling
 - Remove sling
 - Leave sling *in situ*
- Place adjustable sling
 - T-O or Retropubic
- Place artificial urinary sphincter
 - Remove sling
 - Leave sling *in situ*
- ProACT

REPEAT T-O SLING FOR RECURRENT PPI

- 35 patients with mild-moderate SUI after failed first RTS
 - After 16.6 months following repeat sling:
 - 34.5% (10 of 29 patients) - no pad use
 - 37.9% (11 of 29 patients) - 1 dry "security" pad
 - 3.4% (1 of 29 patients) - 1 wet pad
 - 3.4% (1 of 29 patients) - 2 pads
 - 10.3% (3 of 29 patients) - pad reduction $\geq 50\%$
 - 10.4% (3 of 29 patients) - failure.
- After 6 months following repeat sling:
 - 45.5% (15 of 33 patients) - no pad use
 - 30.3% (10 of 33 patients) - 1 dry "security" pad
 - 3% (1 of 33 patients) - 1 wet pad
 - 6.1% (2 of 33 patients) - 2 pads
 - 3% (1 of 33 patients) - pad reduction $\geq 50\%$
 - 12.1% (4 of 33 patients) - treatment failure

Conclusion: Repeat sling is an effective option after failed first sling.

Soljanik et al. Eur Urol, 2010 Nov;58(5):767-72.

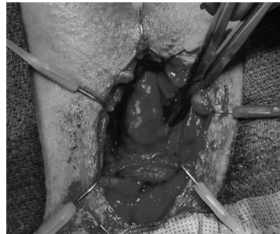
SALVAGE T-O SLING FOR RECURRENT PPI

- 18 patients: Failed early (10), Failed late (8) (>12 months)
 - At 6 m - success (72%), Dry (50%)
 - At 17 m - success (56%), Dry (39%)
 - At 6 m, Late primary failure had better outcome than early (75% vs. 30%; $p = .031$)
- Conclusion: Salvage AdVance male sling is a viable option after a failed primary male sling especially after a prolonged efficacy period.

Martinez et al. UROLOGY. 2015; 85(2): 478-82

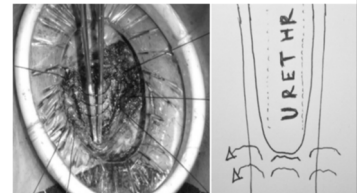
RE-SLING (T-O) PEARLS

- Dissect corpus spongiosum distal to sling
 - Virgin plane
- Identify distal aspect of sling
- Right angle clamp around sling arms
 - Transect sling arms and excise sling off urethra
 - Repair corpus spongiosum with absorbable suture
- Pass new trocars and place sling slightly distal to first sling
 - Chung ASJ et al, Transl Adrol Urol, 2017



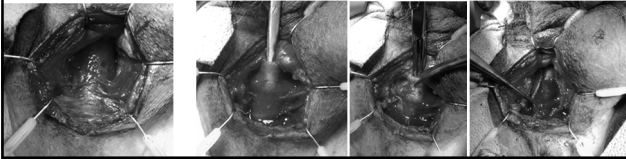
REVISION (QUADRATIC) PEARLS

- Imbrication of prior sling
- Place #1 Prolene plication sutures superficially into fibrous mesh
 - Similar to penile plication imbrication sutures
- Three sutures
 - Initial suture at base of inverted mesh triangle
 - Leading edge of sling
 - Rubin RS, et al: Transl Androl Urol, 2017
- Tensioning via RLPP
 - RLPP measurement and sling fixation improves sling outcome
 - 70% vs 39% much/very much better at 25 months
 - Sourial MW, et al: CUAJ, 2017
 - Comiter, et al, Urology, 2015



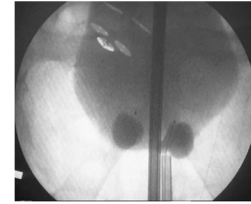
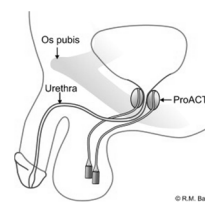
AUS AFTER SLING FAILURE

- Small case series
 - Plenty of personal experience
 - Cure/improve 80%-90%
 - No increase in complication rate
 - Abdou A, Prog Urol, 2012
 - Lenz AC, J Urol 2012
- With prior T-O sling or BAMS
 - Place AUS trans-scrotally or more distally through perineo-scrotal incision
 - Previous sling neither renders surgery more difficult nor affects AUS success
 - Comiter, Neurourol Urolyn, 2005
 - Stakin and Comiter, Campbells Urology, 2006
 - Proximal sling acts a pseudo double cuff
- With prior quadratic sling
 - Divide sling
 - Comiter, Urology, 2015



RECENT APPROVAL OF PROACT

- 10 patients with persistent incontinence after male sling
- At 6 months, all 10 patients dry.
 - Al Najjar, et al, Can Urol Assoc J, 2011



Lehnert, et al: J Urol, 2011

RADIATION AND MALE SLING

- Bulbourethral Northwestern Sling
 - Prior irradiation was the only identified factor that predisposed to sling failure
 - Without radiation – 68% success (37/59)
 - With radiation -29% success (2/7)
 - Schaeffer AJ, J Urol, 1998
- Bone anchored male sling (BAMS)
 - Previous full-course EBRT decreases efficacy of bulbourethral sling
 - Castle, 2005; Onur, 2004; Comiter, 2004
 - Generally 75% BAMS success without XRT
 - Generally ≤50% BAMS success with XRT
- Quadratic sling
 - Scant data
 - Trial did not exclude men with XRT
 - No difference in outcome with and without XRT
 - Comiter, Urology, 2014

RECENT PUBLICATION: RETROURETHRAL SLING +/- XRT

Overall 37 patients, avg f/u 17.3 months
19 (51.4%) dry, 10 (27%) improved, 4 (10.8%) failed

	No XRT	XRT
• Cure	63.3%	• Cure 0%
• Improved	26.7%	• Improved 28.6%
• No change	6.7%	• No change 28.6%
• Worse	3.3%	• Worse 42.9%
• Success	90%	• Success 28.6%
• Failure	10%	• Failure 71.5%

Torrey et al: Urology 82:713, 2013

AUS AND XRT

- Erosion
 - Generally agreed higher erosion rate
 - Risk of erosion has not diminished despite improvement in XRT technique
 - Hird AF, Radomski SB, Can Urol Assoc J, 2015
- Mixed data on continence
 - But with revisions, ultimate success rate is similar
 - Hoy NY, Rourke KF, Urology, 2015
 - Mottet N, et al, Urol Int, 1998
- Recommended to use lower pressure reservoir and/or prolonged deactivation
 - Marlins FE, Boyd SD, J Urol, 1995

Trans-Obturator Sling Advantage over Quadratic Sling

- Easier Technique
- Faster surgery
 - Lowers infection risk
- Potentially less pelvic pain
 - No pain from pubic rami under tension
- Detrusor hypocontractility not a contra-indication

Quadratic Sling Advantages over T-O sling

- Dual mechanism of action
 - T-O – urethral elevation/relocation
 - P-P – urethral compression
- Quadratic fixation more reliable than 2-point fixation
- Broader compression
 - Potentially more efficacious for more severe leakage
- Inside-out passage minimizes risk of urethral injury
- Efficacious for more severe leakage

Trans-Obturator Sling Disadvantages

- Not proven for severe incontinence
- Outside-in passage theoretically risks urethral injury
- Urinary retention rate 3-21%

Quadratic Sling Disadvantages

- High failure rate if fixation fails
- More pain than retroluminal sling
- Need normal detrusor contractility
- Needs to be incised/excised prior to AUS

CLINICAL SCENARIOS WHERE AUS IS PREFERRED

- High volume SUI
 - > 450 g/day
 - Fischer et al 2007
- Prior AUS
 - Sling with poor success post AUS
 - Tuygan et al, 2009; Comiter et al, 2002; Castle et al, 2005
- Dr. or Patient Preference/Predictable success with AUS
 - Best chance of "cure"
 - 90% satisfaction with AUS regardless of degree of incontinence
- History of radiation
 - Sling offers lower rate of success
 - Castle et al, 2005; Onur et al, 2004; Comiter et al, 2004

SLING IS PREFERRED FOR MOST PATIENTS WITH MILD TO MODERATE LEAKAGE

- Intermediate term data with male sling
 - **Sling equally efficacious with lower rate of severe complication in patients with mild-moderate SUI**
 - If they have not failed previous AUS, no xrt, normal bladder contractility
 - 6th ICI, 2018
 - **Patients generally choose sling over AUS**
 - **When given a choice, 92% choose sling**
 - When recommended AUS, 25% still choose sling
 - Kumar A, et al: J Urol, 2008

WHAT SHOULD YOU OFFER ?

- Best to offer what is best, or either if either is OK
 - ISD, weak bladder --- AUS (consider T-O sling if mild)
- Severe incontinence --- AUS
 - Unlikely to have predictable success with T-O sling
 - **Quadratic sling** should be considered for severe leakage if patient refuses AUS
- Moderate leakage, normal bladder -- Quadratic sling
 - AUS still OK after sling failure
 - Sling contra-indicated after AUS failure
- Mild incontinence --- T-O sling
- XRT – AUS
- Revision surgery - AUS

Urinary Fistula in Female Pelvic Reconstruction

Comprehensive Review of Urology
August 7th, 2018

Elise J.B. De, MD
Massachusetts General Hospital

Disclosures

Bloomberg Philanthropies

Grant for "Hope of Hope"

Nothing to disclose



Chair of Education
Committee for ICS

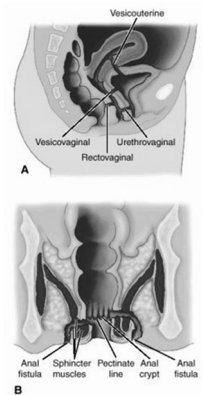
Objectives

- Diagnosis and management of Fistula
- Factors impacting fistula
- Surgical principals surrounding repair

Fistula

Definition: Abnormal communication between two epithelialized surfaces

- Vesicovaginal fistula
- Recto-vaginal fistula
- Urethrovaginal fistula
- Ureterovaginal fistula
- Vesicouterine fistula



Fistula Biology

- All types share a common etiology
- Ischemia / Necrosis
 - Macrovascular
 - Microvascular
 - Infectious
- Impaired Healing
- Poor Nutrition
- Inflammation
- Pressure differential between compartments in context of decreased resistance
- Epithelialization of mature tract

Vesicovaginal Fistula - History

- Egyptian times
 - First mentioned in the Ebers Papyrus
 - Advised against attempts to treat
 - Noted in mummy of Queen Henherit 2050 B.C.
- Avicenna in 950 A.D.
 - Noted correlation between prolonged labor and fistula
- Renaissance Period
 - Term 'Fistula' coined by Luiz de Mercado in 1597
 - Surgical treatment: topical silver nitrate (~ universal failure)
 - Falto: 1st successful repair late 1600s
 - denudation of tract and re-approximation using sharpened swan quills

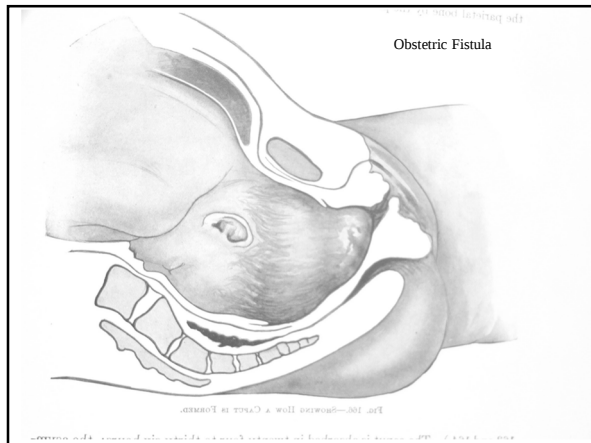
Vesicovaginal Fistula - History

- 1852 Sims
 - successful closure using leaden and silver suture with drainage catheters on his 30th attempt, a slave by the name of Anarcha
- 1861 Collis
 - introduced the concept of a layered closure
- 1890 Trendelenburg
 - pioneered the Transabdominal approach
- 1914 Leguen
 - developed the Transvaginal approach
- 1920 Martius and Garlock
 - developed the concept of interpositional tissues
- 1954 Falk and Trancer
 - recommended routine use of urinary catheter drainage

Etiology of Vesicovaginal Fistula

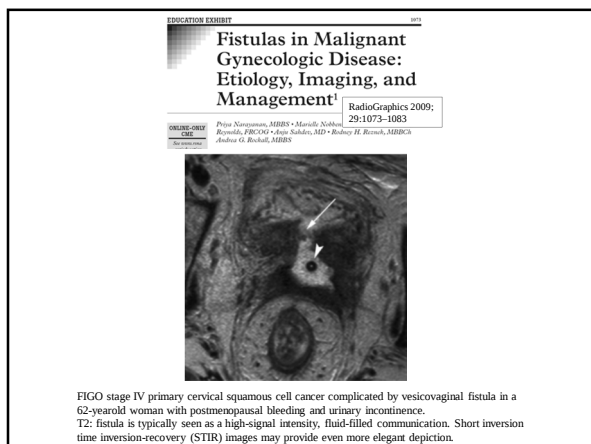
- | | |
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| <ul style="list-style-type: none"> • <u>Developing Countries</u> • Birth Trauma <ul style="list-style-type: none"> – Prolonged Labor – Tissue necrosis of bladder base and urethra with substantial tissue loss • Bilharziasis | <ul style="list-style-type: none"> • <u>Industrialized Nations</u> • 75% due to injury at the time of gynecologic, urologic, or other pelvic surgery (Tancer, 1992). • Most commonly -Inadvertent suture incorporation of vaginal cuff tissue into an unappreciated bladder wall injury • Tissue necrosis promotes fibrosis and induration |
|--|--|

Tancer ML: Observations on prevention and management of vesicovaginal fistula after total hysterectomy. Surg Gynecol Obstet 1992; 175(6):501-506.
Wall LL: Obstetric fistulas in Africa and the developing world: new efforts to solve an age-old problem. Womens Health Issues 1996; 6(4):229-234.
Harris WJ: Early complications of abdominal and vaginal hysterectomy. Obstet Gynecol Survey 1995; 50:795-805.



Other Causes

- Radiation
- Malignancy
- GI Surgery such as Low Anterior Resection
- Inflammatory Bowel Disease
- Urinary Tuberculosis
- Foreign Body
 - Pessaries
 - Birth Control Devices - IUD, Diaphragms
- Autoimmune diseases such as Behcet's (vasculitis-related bladder wall necrosis)
- CO2 Laser Ablation of Cervical Lesions
- Pelvic Fracture (2%)

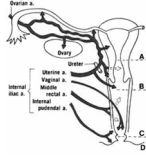


GU Injuries and Hysterectomy

- Ureteral Injury: 6.2/1,000 cases
- Bladder Injury: 10.4/1,000 cases
- Incidence of VV fistula after Hyst: 0.1%
 - 1/1300
 - Highest in Laparoscopic (1/455)
 - Lowest in Vaginal (1/5636)

Ureterovaginal Fistula

- 10% risk of simultaneous ureteral component
- Ureter most likely to be injured at
 - Level of infundibulopelvic ligament
 - Ligation of uterine vessels



Risk Factors for VV Fistula

- Diabetes
- Smoking
- Prior Caesarian Section/Previous Pelvic Surgery
- PID or Concurrent Infection
- Endometriosis
- PVD
- Concurrent Infection
- Malignancy
- Trauma
- Pelvic Radiation
 - Can be seen up to 20 years after irradiation

Presentation of Fistula

- Usually within 7-21 d
- Incontinence
 - Pseudo-Stress
 - Vaginal Voiding (urethrovaginal fistula)
 - Continuous Incontinence – not always
- Ileus
- Pain (ureterovaginal)
- Hematuria
- Vesicouterine: incontinence, amenorrhea, cyclical hematuria

Differential Diagnosis of Post-Hysterectomy Vaginal Drainage

- Fistula
- Posthysterectomy Pseudoincontinence
 - (leakage of peritoneal fluid from a vaginal cuff sinus tract)
- Fallopian Tube Drainage
- Lymphatic Fistula
- True Incontinence
 - Detrusor Instability
 - Poor Bladder Compliance
 - Stress Incontinence
- Vaginal Secretions
- Vaginal Infections
- Vaginal Voiding

Work-up

- Physical Examination
 - Fluid pooled at cuff
 - Identify presence and location of fistula
 - Assess vaginal capacity
 - Evaluate for induration or fibrosis
 - Rule-out pelvic organ prolapse
- Dye Testing (may combine)
 - Tampon Test
 - Oral Pyridium shows as orange on tampon
 - Bladder Instillation
 - With methylene blue or sterile milk
 - Better test for localization
 - Combination can help with ureterovaginal

Work-up

- Cystoscopy
 - Demonstrates size, location, multiple
 - Assesses for edema and necrosis
 - Allows for biopsy if question of malignancy
 - Can be combined with dye testing e.g. Indigo Carmine
- Routine preoperative ureteral imaging
 - RTGP
 - IV Urography
 - RUS misses up to 20% of ureteral injury
- Assess induration, fixation to bone
- Dual balloon catheter (Trattner catheter)
- EUA

Radiographic Evaluation

- VCUG
 - Evaluates for complicating factors such as reflux, cystocele, urethral involvement or urethral diverticulum
- Retrograde Pyelogram
 - Highest diagnostic accuracy for evaluation of ureteral involvement
- MRI

Urethrovaginal Fistula



Urethral Fistula

- Etiologies:
 - Anti-incontinence procedures (mesh)
 - Gynecologic surgery
 - Low Anterior Repair
 - Urethral Diverticulectomy (most common)
 - Urethral catheter trauma
 - Prolonged obstructive labor
 - Pelvic fracture trauma
- Often not apparent until after Foley catheter removed

Urodynamics in Fistula Patients

- Advised by many (including this author)
 - Fistula formation (and recurrence) may be related to bladder factors
 - If further surgical therapy is indicated, can be planned simultaneously
- Over half of women have concomitant findings
 - In a study by Hilton et al. in 1998
 - 47% had stress incontinence
 - 44% had detrusor instability
 - 17% had poor bladder compliance

Pre-Op Endoscopic Evaluation

- Cystoscopy
- Retrograde Pyelograms
- Speculum Exam with:
 - Lonstar Retractor
 - Methylene Blue
- Plan Formal Repair Thereafter

Obstetric Fistula

- Prior to 1900, the most common cause of VVF in the U.S. was obstructed labor (Stothers et al, 1996)
- In the developing world, VVF most commonly occur as a result of prolonged obstructed labor due to cephalopelvic disproportion, with resulting pressure necrosis (Arrowsmith et al, 1996)
- “Obstructed labor injury complex”: urethral loss, stress incontinence, hydronephrosis, renal failure, rectovaginal fistula, rectal atresia, anal sphincter incompetence, cervical destruction, amenorrhea, pelvic inflammatory disease, secondary infertility, vaginal stenosis, osteitis pubis, and foot drop (Arrowsmith et al, 1996).

Arrowsmith SD: Genitourinary reconstruction in obstetric fistulae. J Urol 1994; 152(2 Pt. 1):403-406
Stothers L, Chopra A, Raz S: Vesicovaginal fistula. In: Raz S, ed. Female urology, 2nd ed. Philadelphia: WB Saunders; 1996:490-506.

Obstetric Fistula

- Some estimates place the worldwide prevalence as high as 2 million women worldwide.
- In some rural areas of Africa, the fistula rate may approach 5-10 per 1000 deliveries, which is close to the maternal mortality rate in Africa.
- An estimate of up to 500,000 new cases of obstetric fistula occur throughout the world annually (Hilton, 2003), although the total morbidity from obstructed maternal labor has been estimated to be in excess of 5 million individuals annually (Kelly, 1991)
- 96.5% of 932 VVF seen at a single hospital in Nigeria over a 7-year period were temporally associated with labor and delivery (Wall et al, 2004).

Wall L, Arrowomith S, Briggs ND, Browning A, Lassey A. The obstetric vesicovaginal fistula in the developing world. In: PA, L, C, S K, A W, editors. *Incontinence*. Paris: Health Publications; 2005. p. 1403-54.
Wall LL. Obstetric fistulas in Africa and the developing world: new efforts to solve an age-old problem. *Womens Health Issues* 1996; 6(4):229-234.

Fistula Worldwide

- Cephalopelvic disproportion:
 - Fetus is impacted 3 to 5 days
 - Fetus dies 85% of the time leading to softening and delivery
 - The woman, if she survives, can be left with a fistula
- Other etiologies:
 - Trauma
 - Sexual abuse
 - Coital injury in child brides
 - Female genital mutilation



Hilton P. Vesico-vaginal fistulae in developing countries. *Int J Gynaecol Obstet* 2003; 82(3):285-295
Kelly J. Fistulae of obstetric origin. *Midwifery* 1991; 7(2):71-73

United Nations Population Fund (UNFPA) and the
United Nations International Children's Educational Fund (UNICEF) Survey:

- Each African country surveyed had only one emergency obstetric center per 500,000 inhabitants
- Only 8-35% of women with complications during labor received care at an appropriate facility
- Even when the patient arrives at the facility, good care is not a guarantee. Most emergency care requires payment.

Lewis G, deBernis L, editors. *Obstetric fistula: guiding principles for clinical management and programme development*. Geneva, Switzerland.: WHO; 2006. p. 78.

Maine's Three Delays

- **1-Delays in the decision to seek care** influenced by socio-economic and cultural factors (need to obtain permission from a husband or male family member to seek care)
- **2- Delayed arrival at the health facility** (Road conditions, transportation and communication deficiencies)
- **3- Delayed provisions of adequate care** at the facility may be due to lack of staff, supplies, or electricity or inability to reach a surgeon



Fistula



- Estrangement from spouse / social life. Patients often live with willing relatives
- In addition to discomfort from the continuous soiling, these women are often rejected by their husband, their family and their community. They cannot use transportation, walk for long periods of time, stand outside with friends, cook, participate in social and religious events, or go to the mosque or church.
- Since most of these women are left without children, they feel that they cannot fulfill their role as a woman, a wife or a mother. Most have trouble finding work. The combination of social and economic forces in many of these cases compounds the woman's preexisting poverty, and malnourishment is the rule. These physical and psychological factors impact the success of surgery in the percentage of women who find treatment.

Incidence & Risk factors Obstetric fistula

- Between 0.1% to 1.5/1,000 deliveries in rural areas.

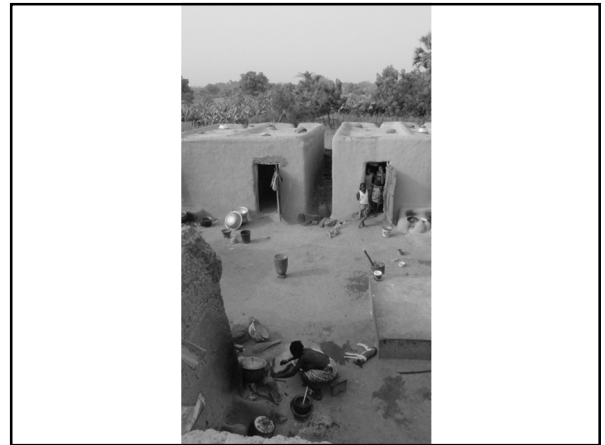
Major risk factors appear to be:

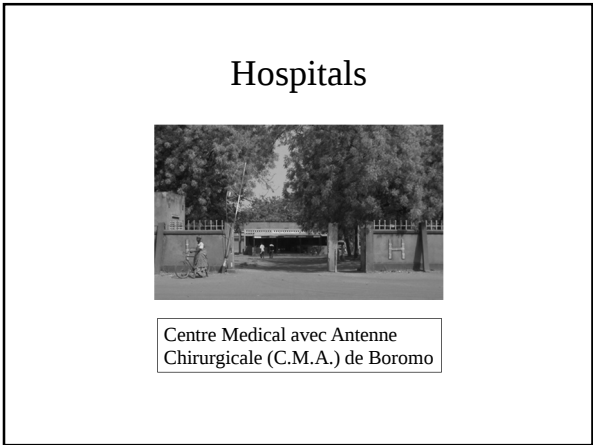
- Age at first marriage
- Short stature
- Pregnancy with a male child
- Failure to attend antenatal care
- Low socio-economic status
- Low social class
- Lack of employment and illiteracy.



Setting for Delivery

- Wife lives with husband's family
- Mother in law or 1st wife attends delivery
- Distance to C section is 1 day walk





Many Developing Facilities Lacking

- Diagnostics
 - Urodynamics
 - CT
 - MRI
- Medications
 - Anticholinergics
 - Antibiotics
 - Botox
- Supplies
 - CIC
 - Irrigation (e.g. Augment)
- Sophisticated techniques
 - Augment, Catheterizeable stoma, AUS
- Physiotherapists/ Nurses
 - Voiding dysfunction not addressed



Facilities



Int Urogynecol J (2015) 26:749–755
DOI 10.1007/s00192-014-2575-7

ORIGINAL ARTICLE

Validation of a culturally compliant voiding platform for urodynamics in African vesicovaginal fistula patients

Ali Borazjani • Helina Tadesse • Fekade Ayenachew • Howard B. Goldman • Margot S. Damaser • L. Lewis Wall

Only the heel-to-heel distance (H-H) measure of posture was significantly increased on the platform compared with on the ground.

Management

Conservative Management

- Urethral Catheter Drainage and Anticholinergics
- Success less likely with
 - mature tracts (>7 d)
 - Large defects > 5-10 mm
 - Malignancy or radiation
- Success rate 2-20 %
 - Trancer 1992
 - Dmchowski 2006
 - Telinde's Operative Gynecology 7TH ed. 1992

Cystoscopic Treatment

- Fulguration
 - 73% success rate with fistulas <3mm in size
 - 2 weeks of catheter drainage post-op
 - -Stovsky 1994
- Cystoscopically placed suture closure described by McKay in 1997
 - Has not gained popularity

Fibrin Glue

- Use of fibrin glue as an interpositioning layer during the vaginal anatomical repair of complicated vaginal fistulas
- Alternative to the use of Martius flaps interpositioning.
- Decreases operative time and adding simplicity to the already complicated procedure are additional values of using this procedure.

Safan A, Shaker H, Abdelal A, Mourad MS, Albaz M. Fibrin glue versus martius flap interpositioning in the repair of complicated obstetric vesicovaginal fistula. A prospective multi-institution randomized trial. *Neurourology*. 2009;28(5):438-41.

Fistula Repair Standard Principles

- First operation is best chance
- Ureters should be evaluated identified and protected
- Fistula should be widely mobilized, closed without tension
- Repair must be water-tight and infection free
- Martius flap or other graft should be considered in complex cases.
- Evaluate sphincteric mechanism (anti-incontinence ?later).
- Associated Vagino-rectal fistulae (repaired simultaneously ± colostomy).
- After repair, drain 10-14 days

Simple Fistula

- 20% of obstetric fistulas are simple.
- Less than 3 cm in diameter
- No or only mild scarring
- Do not involve the urethra.

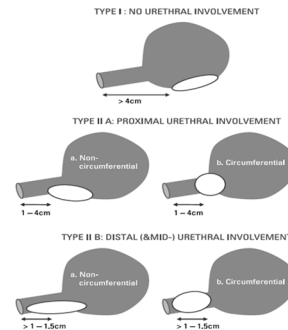
Johnson K. *Int J Gynaecol Obstet*. 2007 Nov;99(suppl 1):5122-9.
Naidu PM. *J ObstetGynaecol Br Emp*. 1962 Apr;69:311-6.
Aziz SA. *J ObstetGynaecol Br Communw*. 1965 Oct;72(5):765-8.
Adeniyi TL. *West Afr Med J Niger Med Dent Pract*. 1973 Apr;22(2):39-43.
Waldijk K. The (surgical) management of bladder fistula in 775 women in northern Nigeria (Doctoral). Utrecht, Netherlands: Utrecht; 1989.
Arrowsmith SD. *J Urol*. 1994 Aug;152(2 Pt 1):403-6.
Krichman RG. *J ObstetGynaecol Br Emp*. 1949 Feb;56(1):22-7.
Albert DH. *East Afr Med J*. 1950 Mar;27(3):149-16.
Lavery DW. *J ObstetGynaecol Br Emp*. 1955 Aug;62(4):530-9.
Mahfouz N. *J ObstetGynaecol Br Emp*. 1957 Feb;64(1):23-34.
Hamlin RH. *Nicholson EC. Ethiopian Medical Journal*. 1966;4(2):189-92.

Complex Fistula

- > 4-5 cm in diameter
- Involvement of urethra, ureter, rectum
- Juxtacervical – with incomplete visualization of the superior edge
- Previous Failed Repair

Classification

Waldijk classification



Surgical Therapy

- “First attempt is most likely to succeed”
 - 1st attempts meet with 90% success
 - Factors that affect success
 - Etiology
 - Duration
 - Presence of necrosis or infection
 - Surgeon experience
- Dmochowski 2006

Timing of Repair

- Classic Dogma
 - Wait 3 to 6 months before surgical attempt at closure
 - Those encountered in first two days should be immediately repaired
- Some now trying earlier repairs
 - Transvaginal approach to apical fistula success in 94% in patients up to 6 weeks out from injury
 - Select patients
 - Not done immediately post-op

Hadley et al 1990

Preoperative Preparation

- Treat any Infections
- Antibiotics
- Estrogen replacement if indicated for 4 to 6 weeks pre-op

Surgical Approaches

- | | |
|--|--|
| <ul style="list-style-type: none"> • <u>Transvaginal</u> <ul style="list-style-type: none"> – Associated with decreased operative time – Less morbidity – More rapid recovery – Difficult with fibrosis or pelvic immobility – Difficult with larger defects – Greater risk of ureteral injury | <ul style="list-style-type: none"> • <u>Abdominal</u> <ul style="list-style-type: none"> – Better with a poorly visualized tract – Difficult with a narrow or immobile vagina – Easier for large defects – Allows other procedures at same time (e.g. reimplant) – Less risk of ureteral injury |
|--|--|

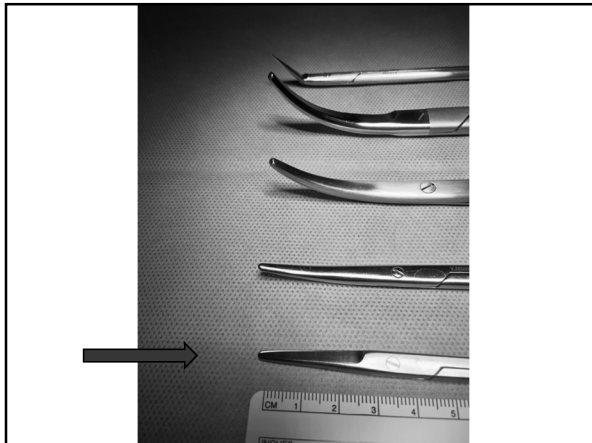
Vaginal Approach

- Catheters
 - Suprapubic
 - Urethral
 - Ureteral
- Intraoperative Cystoscopy
- Self retaining retractor
- Small balloon catheter through fistula tract
- U or J type Vaginal incision incorporating base of fistula tract into the flap
- Vaginal mucosal flap oriented anteriorly
- Lateral relaxing incisions often required

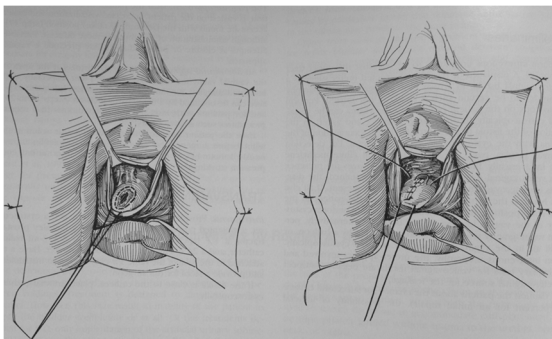


Vaginal Approach

- Fistula tract circumscribed but not widely excised to avoid a wide defect
- Wall opposite flap dissected to allow advancement of flap beyond defect
- Fistula tract closed with full thickness bites of bladder (1st layer)
- Second layer is prevesical fascia closed at a 90 degree angle
- Flap is an option
- Integrity is tested by filling the bladder
- Third layer closed by advancement of vaginal tissue over suture lines

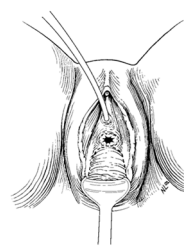


Multilayer Vaginal Approach



Hinman 1998

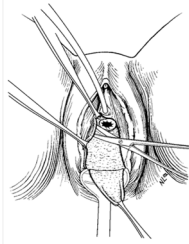
Transvaginal VVF



- Distal mid-trigonal fistula
- Amenable to transvaginal repair
- Maximal drainage – suprapubic and urethral Foley

Transvaginal VVF - 2

- Development of U-flap with the fistula forming the apex
- Advancement of the vaginal flap at the completion of the procedure



U Flap



Transvaginal VVF

- 1st layer- Transverse closure of the fistula including the tract (without excision); interrupted 3-0 or 4-0 vicryl
- 2nd layer – imbrication of perivesical fascia

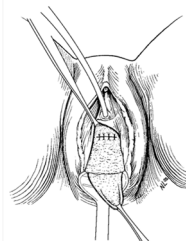
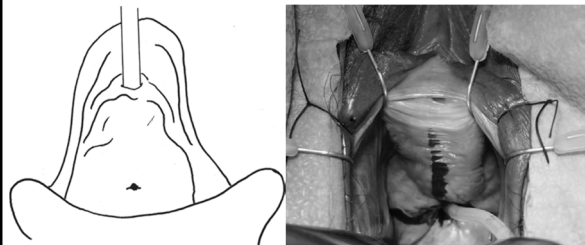


Fig. 17.1

(a) Fistula exposure.

(b) Foley catheter within fistula can apply traction. Note the inverted T incision



Chapter 17 Vesicovaginal Fistula Repair Christopher K. Payne. In: Zimmern P, Die E ed: Native Tissue Repair for Incontinence and Prolapse. Case-based technique with video demonstrations. Springer Switzerland. Copyright 2017

Fig. 17.2 Circumscribing incision of fistula tract

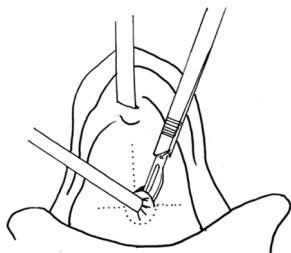


Fig. 17.3 Dissection of proximal flap

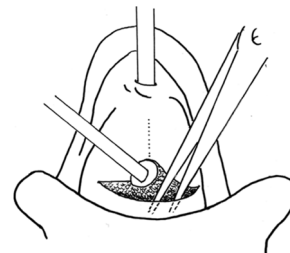


Fig. 17.4 Proximal flap is dissected to the apex and lateral flaps to the pelvic sidewall. Observe the 2 cm radius around the fistula

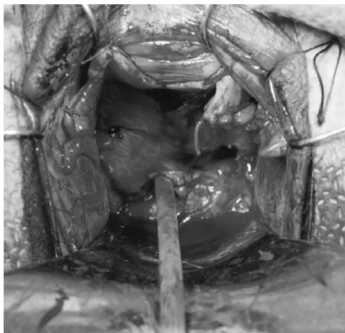


Fig. 17.5
(a) Beginning fistula closure.
(b) Full thickness sutures are placed at each pole of the fistula closure, taking care to include the bladder mucosa. The orientation is chosen so as to optimize a low tension closure. Interrupted sutures are then continued to complete the closure

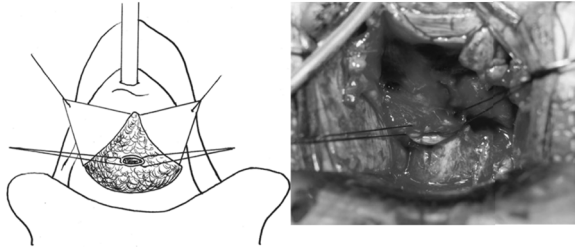
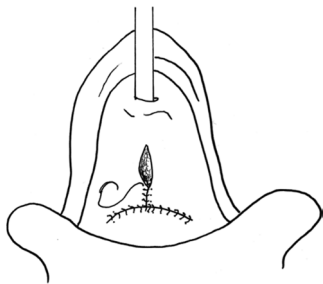


Fig. 17.6 Skin closure. In many cases the posterior flap can be advanced much farther anteriorly when there would otherwise be inadequate skin to close without tension. Always debride any questionably viable skin edges



Is vascularized tissue necessary?

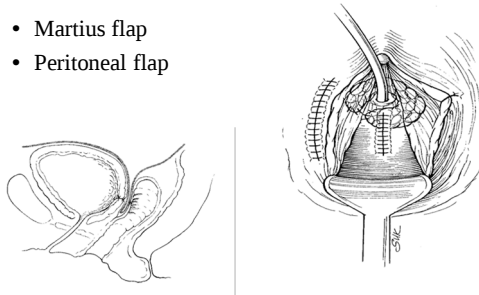
- Fistula size > 2 cm
- Recurrent fistula
- Radiation

Eilber KS, et al. J Urol 169, 1033–1036, March 2003

	Abdominal Approach	Vaginal Approach
Use of adjunctive flaps	Omentum, peritoneal flap, rectus abdominus flap	Labial fat pad (Martius fat pad), peritoneal flap, gluteal skin or gracilis myocutaneous flap
Relative indications	Large fistulae, location high in a deep narrow vagina, radiation fistulae, failed transvaginal approach, small-capacity bladder requiring augmentation, need for ureteral reimplantation, inability to place patient in the lithotomy position	Uncomplicated fistulae, low fistulae

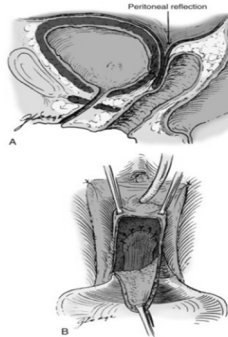
Flap Interposition – Vaginal Approach

- Martius flap
- Peritoneal flap

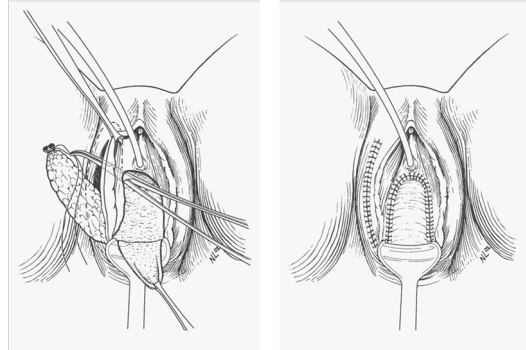


Flaps (vaginal approach)

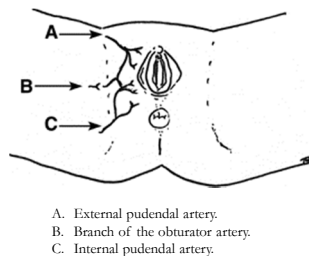
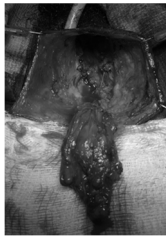
- S. Raz- peritoneal flap



Martius Graft



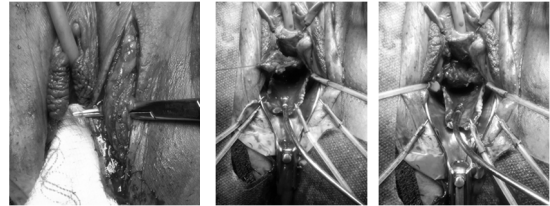
Martius Flap



- A. External pudendal artery.
B. Branch of the obturator artery.
C. Internal pudendal artery.

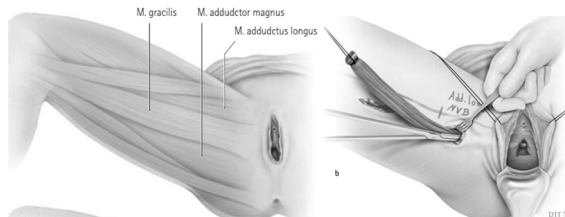
Gynecology and Obstetrics Lippincott Williams and Wilkins 2004.
Chapter 90 Vesicovaginal and Urethrovaginal Fistulas
Ted M. Roth and G. Rodney Meeks

Martius



Flaps (vaginal approach)

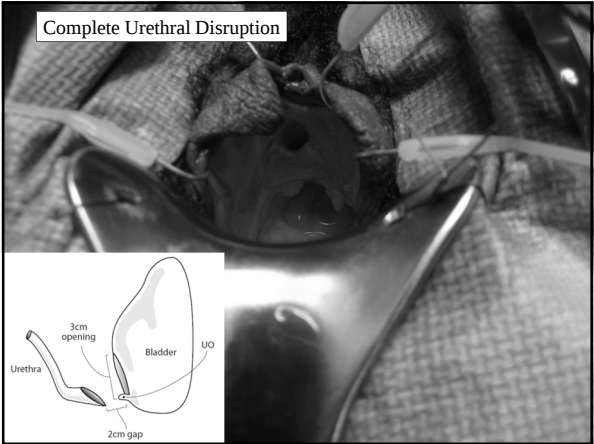
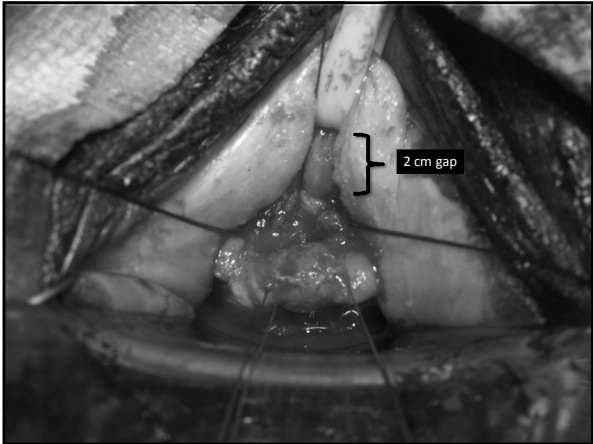
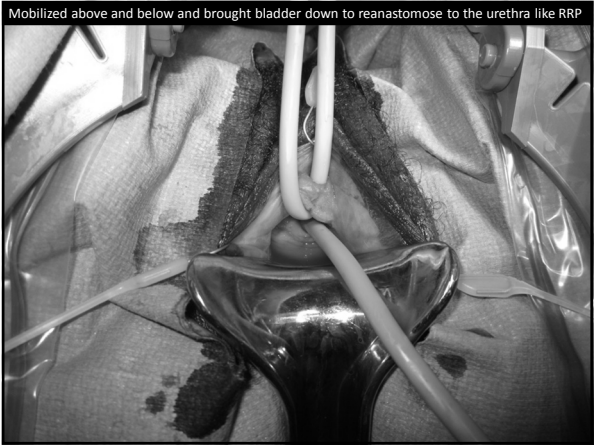
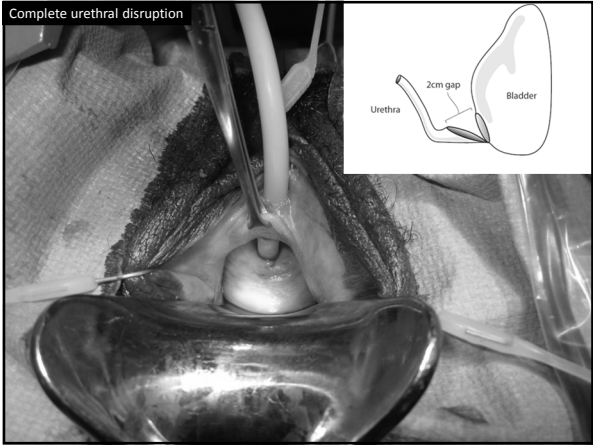
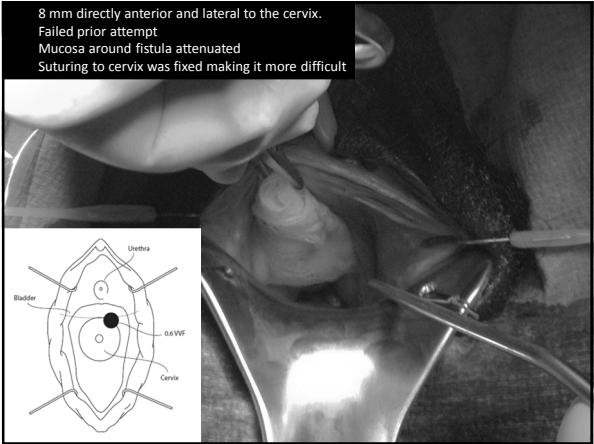
- Garlock 1928- Gracilis myocutaneous flap

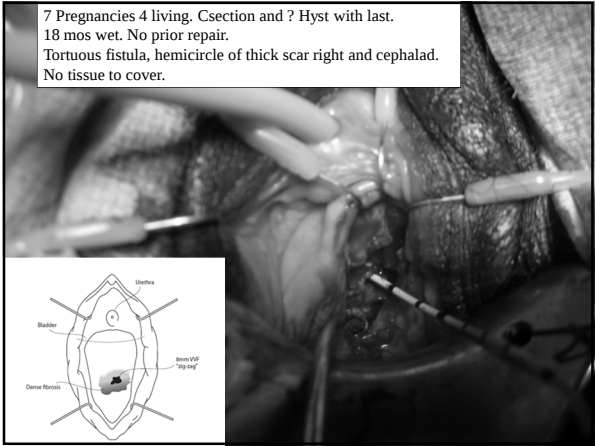
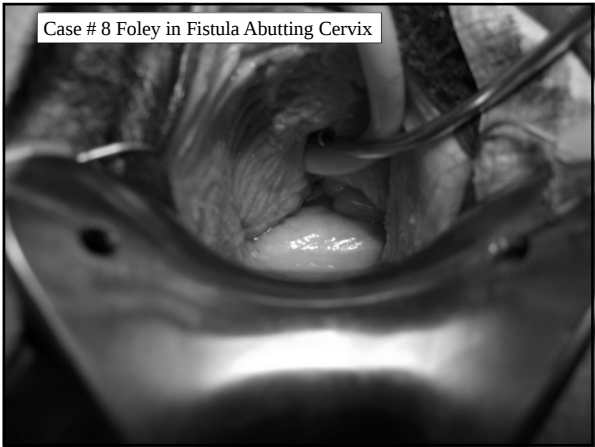


Surgery Illustrated - Surgical Atlas
Repair of giant vesico-vaginal fistulae using a
rotational bladder flap with or without a gracilis flap
Viet Q. Tran, Mohamed Elzein and Sherif R. Abouel

Alternative Vaginal Procedure

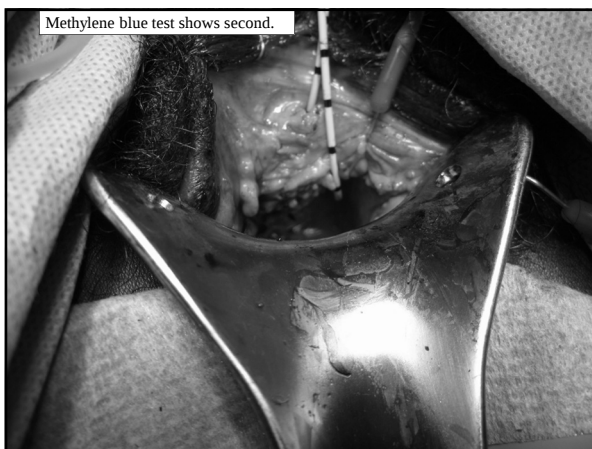
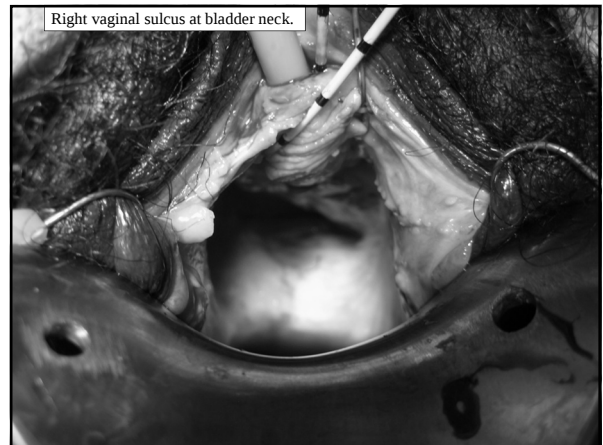
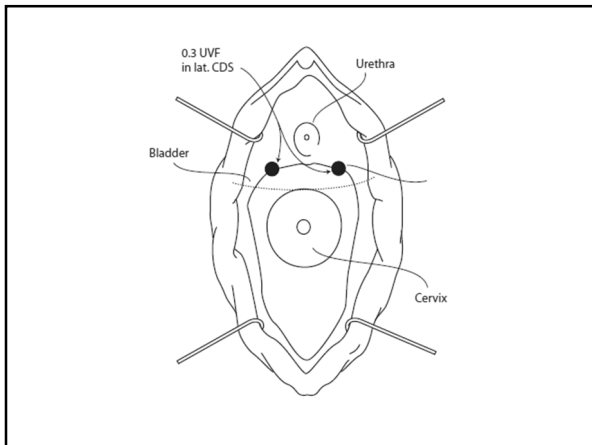
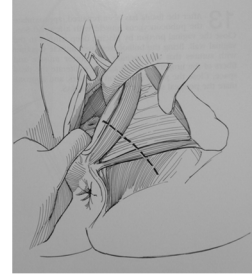
- For poor operative candidates or those with deep and elastic vagina
 - Excision of epithelium around the fistula site
 - Colpocleisis - several layers of suture across the vaginal walls, obliterating the vagina around the fistula
 - Vaginal depth is compromised by this
 - +/- Dyspareunia







Schuchardt Perineal Incision



Postop Care

- Bladder relaxation with anticholinergics
- Catheter drainage 3 weeks
- VCUG to confirm closure then foley removed
- If drainage resumes when foley is removed replace
- No intercourse for 2 months
- Continue estrogens

Success Rates Obstetric Fistula

- The advantage of having the fistula well repaired the first time is crucial because success rate decreases with more attempts of repair:
 - - First repair success rate: 70-90%
 - - 2nd repair success rate: 50-60%
 - - >than 2 procedures: <40%

Mourad, Chapter 18

Risk factors for persistent incontinence:

- 1) Urethral Involvement (OR 8.4)
- 2) Large Fistula (OR 1.3 for each cm)
- 3) Severe vaginal scarring (OR 2.4)
- 4) Small bladder size (OR 4.1)
 - Of note, patients cannot afford anticholinergics

Browning A. Risk factors for developing residual urinary incontinence after obstetric fistula repair. BJOG 2006; 113:482-485.

In patients in whom all of the risk factors mentioned above are present, the postoperative incontinence rate may approach 100% [,35].

Success

- Fistulas can be closed successfully in 72% to 92% of cases. The definition of success, however, is often different when the perspectives of the patient and the surgeon are compared. "Success" to a fistula patient means complete restoration of urinary continence and control, whereas many surgeons define "success" as simply closing the fistula
- Estimates of persistent urinary incontinence after a successful closure of the fistula:
 - 16.3% in a large retrospective review of patients by Wall et al
 - 33% in a small series of complex fistulas in which the proximal urethra was lost

Wall L, Arrowsmith S, Briggs ND, Browning A, Lassey A. Fistula in the developing world. In: P.A. L.C. S.K. A.W. editors. Incontinence. Paris: Health Publications; 2005. p. 1403-54.
Genadry RR, Creanga AA, Roennelung ML, Wheelless CR. . Int J Gynaecol Obstet. 2007 Nov;99Suppl1:551-6.

Complications

- Cicatrix leading to:
 - Vaginal stenosis and
 - Dyspareunia
- Persistent Fistula
 - Secondary repair to be done only after post-op inflammation has resolved

Urethral Fistula Repair

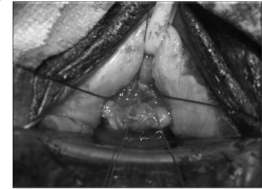
- Distal
 - Extended meatotomy
- Small to Intermediate
 - Tension-free layered closure
- Debilitated patients
 - Bladder neck closure with catheterizable stoma
 - Circumferential closure at bladder neck by complete disruption of the endopelvic fascia & layered inverting closure of the urethral stump

Surgical Repair Urethrovaginal Fistula

- Suprapubic tube recommended
- Inverted U or J incision
- Flap raised to level of bladder neck
- Lateral dissection should be accomplished to perforate the endopelvic fascia for purposes of placement of sling or suspension sutures
- Fistula tract circumscribed but not excised
- Margins apposed with running 3-0 or 4-0
- Second layer incorporates periurethral tissues
- Vaginal flap closure
- +/- Interposition tissue

Vaginal Flap Urethral Reconstruction

- 14 Fr urethral catheter placed
- Inverted U with apex just proximal to the meatus
- Neourethra created using 2 parallel incisions on either side of the meatus
- Flaps are mobilized laterally and tubularized around the catheter
- Closed with a running locking 4-0 suture
- Interposition tissue utilized



Concomitant Sling

- Beneficial effects on urethral function (closure)
- Also adds interpositional tissue
- Some advise empiric placement given high rate of stress incontinence

Outcomes

- 50% dry without a simultaneous anti-incontinence procedure
– Khanna 1992
- 87% continent with sling
– -Blaivas et al. 1996
- Urethral stricture may result

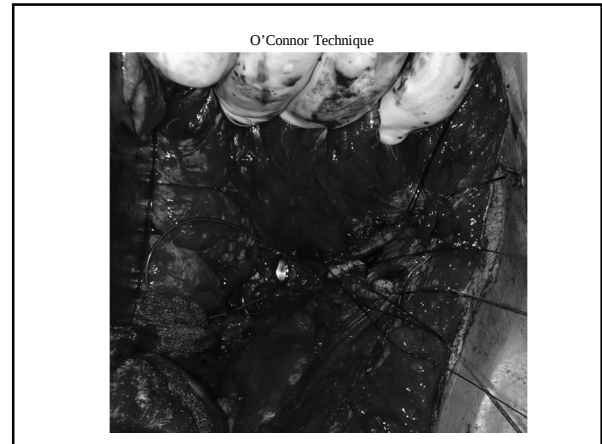
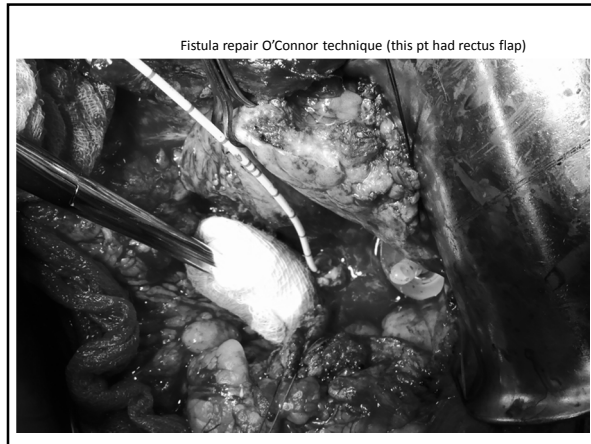
Abdominal Technique

- Does not work for fistulas extending to the urethra
- Good for bladder concurrent augmentation or reimplantation
- May be approached extra-peritoneal or intraperitoneal with bisection of the bladder to the level of the fistula.
- Ureteral catheterization.
- Bladder and vagina are mobilized and separated by dissection along the vesicovaginal septum (difficult)
- Tract is completely excised
- Posterior bladder flap mobilized to repair vaginal defect
- Interposition of omentum if intraperitoneal

Transabdominal Repair (O'Connor)



- Traditional approach – large cystotomy to the level of the fistula
- Development of space between the cystotomy and vaginal side of fistulous tract



Transabdominal VVF

- Placement of omental flap, if available
 - Peritoneum
 - Porcine Dermis

Flaps (abdominal approach)

- Turner-Warwick 1972: omental flap
- Based on Rt. gastroepiploic pedicle

Surgical principles of omentoplasty in urology

Philippe Paparel, Jean-Louis Caillot*, Paul Perrin and Alain Ruffion

2007 BJU INTERNATIONAL | 99, 1191-1196 |

Flaps (abdominal approach)

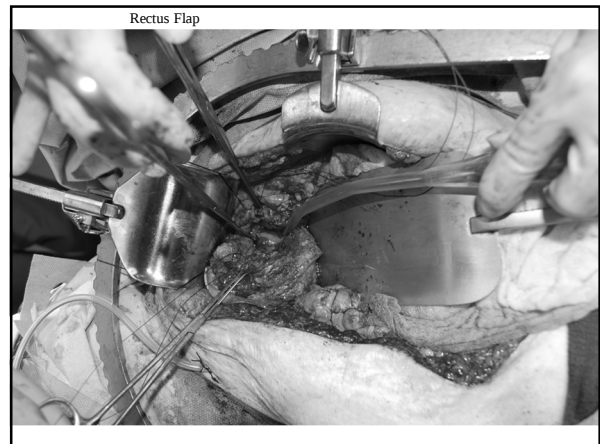
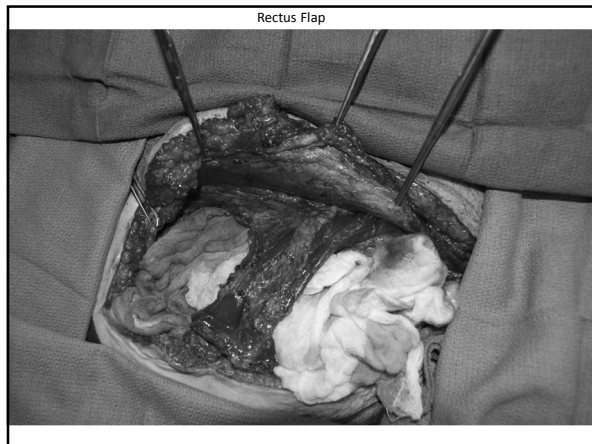
- Ingelman-Sundberg 1960- rectus abdominis
- Based on inferior epigastric pedicle

2005 BJU INTERNATIONAL | 95, 450-451 |

Use of a pedicled rectus abdominis muscle flap to protect against fistula formation after bladder neck closure

JOHN S. MCGRAW AND SARAH A. MACKENNOT

BRUCE RE. USE OF RECTUS ABDOMINIS MUSCLE FLAP FOR THE TREATMENT OF COMPLEX AND REFRACTORY RETROVAGINAL FISTULAS. J. UROL. 2000 163, 1212-5.



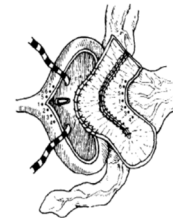
Tissue Loss

- In some cases pressure necrosis may destroy virtually the entire bladder, so that if the defect can be closed at all, the afflicted woman is left with a remarkably small (30 - 50 ml) bladder that compliance may be altered by the extensive fibrotic changes that often take place.
- To date there have been few urodynamic studies reported on patients who have undergone successful fistula closure

Schleicher DJ, Ojengbede OHA. International Urogynecology Journal 1993;4:262-5.
Carey MP, Goh JT, Fynes MM, Murray CJ. Am J Obstet Gynecol. 2002 May;186(5):948-53.

Compliance/Capacity

- Integration of **augmentation** into the repair of the fistula
- Diversion
 - +/- cath stoma
 - +/- cystectomy



Tabakov ID, Slavchev BN. J Urol 171, 272-274, January 2004

Cervical Cancer

- Retrospective review 2096 pts treated for cervical cancer /10 y
 - 38 patients (1.8%) developed fistula (Emmett et al)
 - All had undergone previous radiation therapy.
- Reported annual incidence of XRT- VVF 1%-5% (Angioli)
- May occur up to 30 years after XRT treatment (Zoubek et al)

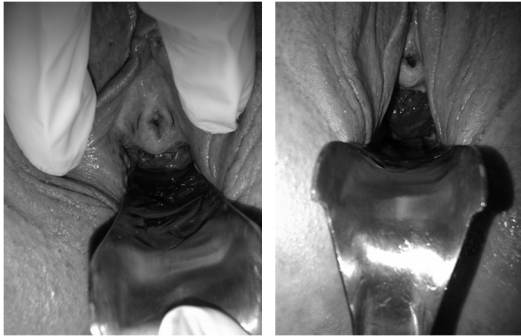
Emmett C, Kohler U. Arch Gynecol Obstet 1996;259:19-24.
Angioli R, Penalver M, Muzii L, et al. Crit Rev Oncol Hematol 2003;48:295-304.
Zoubek J, McGuire EJ, DeLancey JO. J Urol 1989;141:1347-1349.

Exenterative Surgery

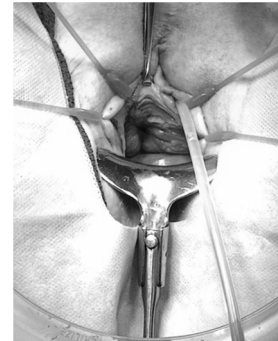
- Retrospective review spanning 45 years (Berek et al, UCLA):
 - Among 75 patients who underwent exenterative surgery (most of whom simultaneously underwent reconstruction of the bladder, vagina, or colon)
 - 17 (23%) developed intestinal or urinary tract fistulas.
- Postoperative fistulas typically occur 10-20 days after surgery (Avritscher) but also may manifest in the immediate postsurgical period.

Berek JS, Howe C, Lagasse LD, Hacker NF. Gynecol Oncol 2005;99:153-159.
Avritscher R, Madoff DC, Ramirez PT, et al. RadioGraphics 2004;24(suppl 1):S217-S236.

Neobladder Fistula



Neobladder Fistula

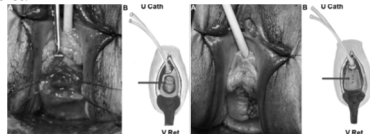


Reconstructive Urology UROLOGY 81 (1), 2013

Vaginal Repair of Pouch-vaginal Fistula After Orthotopic Bladder Substitution in Women

Badr Al-Eid and Alhail Ashamallah

- 298 women underwent orthotopic neobladder after radical cystectomy.
- 8 PVF (2.7%) were diagnosed
 - 5 of 100 (5%) before and
 - 3 of 198 (1.5%) after technical modifications (to be discussed).
- Transabdominal repair 2 and vaginal repair in 6
- At mean 146 months:
 - All repaired patients were continent
 - 1 had nocturnal incontinence.



Unpublished J
DOI: 10.1007/978-94-007-1036-4

CASE REPORT

Vaginal repair of neobladder–vaginal fistula: a case report and review of the literature

Katherine Geller · Justin Bohrer · Charles O. Kim · Steven Mungale

- Bestard Vallejo [23]: 8-mm fistula at the urethro–ileal anastomosis:
 - Vaginal approach using a two-layer closure
 - Martius flap interposition
 - No reappearance after 1 year.
- Pruthi et al. [15]: two patients who developed NVF after collagen
 - NVFs at the level of the bladder neck were repaired transvaginally
 - 3 layers and Martius flap interposition
 - Cadaveric fascia pubovaginal sling with infrapubic bone anchors
- Successful experiences using omental, peritoneal, or (Martius) flaps [19–21].

Modifications

Unpublished J
DOI: 10.1007/978-94-007-1036-4

Vaginal repair of neobladder–vaginal fistula: a case report and review of the literature

Katherine Geller · Justin Bohrer · Charles O. Kim · Steven Mungale

- Risk of injury greatest:
 - Most distal dissection of the vesico-vaginal plane near urethra
 - Poor vascularity or radiation therapy
- Prior recommendations:
 - Dissect urethral and vaginal stumps separately to have easy anastomosis
 - Minimize blunt dissection in the vicinity of the bladder neck and sharply dissect the posterior urethra
 - Preserving the anterior vaginal wall during cystectomy
 - Avoid overlapping suture line between vagina and bladder neck
 - Omental flap interposition may help to avoid future fistulization

Kumar A, et al, 2009: Saudi J Kidney Dis Transpl 20:658–661
Rapp DE et al, 2004: BJU Int 94:1092–2095

EUROPEAN UROLOGY 55 (2009) 131–138

available at www.sciencedirect.com
journal homepage: www.elsevier.com/locate/euro

EAU

Surgery in Motion

Management of Radiation-Induced Vesicovaginal Fistula

Dmitri Y. Pushkar*, Vladimir V. Dyubov, Georg R. Kasyan

Department of Urology, Moscow State Medical Stomatological University, 127096, 21/3, Vorontskaya, Moscow, Russia

- Pelvic radiation: primary cause of delayed vesicovaginal fistula
- Fibrosis occurs in the bladder lamina propria.
- Hyalinization of the connective tissues (radiation fibroblasts)
- Small and medium arteries: obliterative arteritis.
- Atrophy or necrosis of the bladder epithelium
- Ulceration or fissures form.
- Majority present 1.5–2 yr after radiotherapy

EUROPEAN UROLOGY 55 (2009) 131–138

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journal homepage: www.elsevier.com/locate/euro

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Surgery in Motion

Management of Radiation-Induced Vesicovaginal Fistula

Dmitri Y. Pushkar*, Vladimir V. Dyakov, Georg R. Kasyan
Department of Urology, Moscow State Medical Stomatological University, 127086, 25/3, Yushkova, Moscow, Russia

Pre-operative Workup:

- Biopsies are obligatory – must prove there is no malignant recurrence.
- Upper urinary tract functions should be carefully evaluated.
- Intravenous or retrograde urogram
- Cystoscopy
 - Demonstrate the location and size of the fistula
 - Assess bladder mucosa – edema, necrosis
 - In most cases, ureteral injuries due to radiation are limited to sclerosis of paraureteral tissues and obliteration of lower ureters or ureteral orifices.
 - In some cases, ureteral orifices appear on the edges of vesicovaginal fistula.

EUROPEAN UROLOGY 55 (2009) 131–138

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Department of Urology, Moscow State Medical Stomatological University, 127086, 25/3, Yushkova, Moscow, Russia

- 216 patients
 - Vaginal approach in 210 (97.2%), abdominal approach in 6 (2.8%).
 - Martius flap 41.0% of cases (86/210)
 - Latzko colpocleisis 35.7% of cases (75/210)
- Primary RVVF repair was effective in 48.1% patients (101/210).
 - Secondary repair performed in 98 of the 110 failures
 - Cumulative success rate reaching 66.6%
 - Tertiary surgery in 42 patients
 - 19 patients had more than three operations.
- Overall efficiency of 80.4%. 169 patients out of 210

EUROPEAN UROLOGY 55 (2009) 131–138

available at www.sciencedirect.com
journal homepage: www.elsevier.com/locate/euro

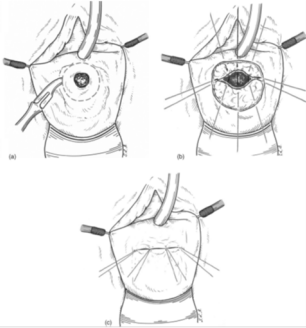
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Department of Urology, Moscow State Medical Stomatological University, 127086, 25/3, Yushkova, Moscow, Russia

- Vaginal and bladder walls surrounding the fistula are scarred
- Excision of the fibrotic tissues would result in large defects
- Latzko colpocleisis should be applied.



Radiated Fistulas

- Periodically assess pre-op given propensity of these to evolve over time
- Wide excision and tissue interposition
- Fistulas may occur up to 20 y following XRT
- Gracilis Flap best interposition tissue
- 50% -80 % success
 - Raz 1992
 - Bissada 1998

Timing of Repair after Radiation Fistula

- Allow for resolution of necrosis and inflammation – up to 1 year
- Strongly consider interposition of vascularized tissue
- Success rates 40-100% (Level 3 Evidence)
- Assess bladder compliance, consider augment or diversion

Angioli et al. Critical Reviews in Oncology/Hematology; 48: 2003; 295.

Thank you!



Non Hysterectomy Fistula

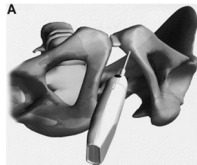
- Tend to be complex
- Understanding the underlying disease process and the surgical principles for repair are key
- Workup of bladder function / ureters follows the same principles as in hysterectomy fistula

Spontaneous Fistula

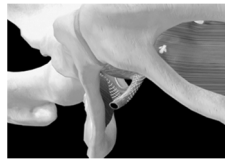


Sling for Stress Incontinence

Bone anchored sling



Modified Miniarc

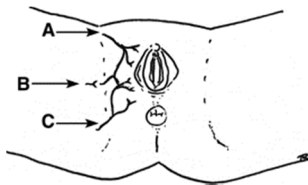
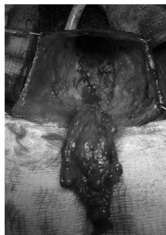


Courtesy AMS

Surgical Therapy

- “First attempt is most likely to succeed”
 - 1st attempts meet with 90% success
 - Factors that affect success
 - Etiology
 - Duration
 - Presence of necrosis or infection
 - Surgeon experience
- Dmchowski 2006

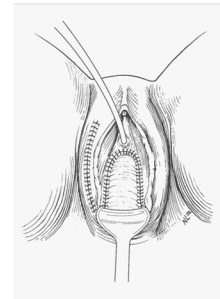
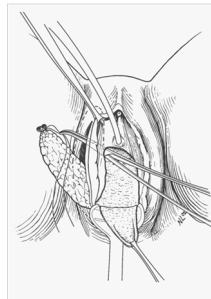
Martius Flap



- A. External pudendal artery.
B. Branch of the obturator artery.
C. Internal pudendal artery.

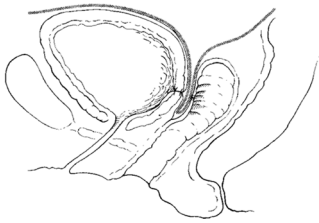
Gynecology and Obstetrics Lippincott Williams and Wilkins 2004.
Chapter 90 Vesicovaginal and Urethrovaginal Fistulas
Ted M. Roth and G. Rodney Meeks

Martius Graft

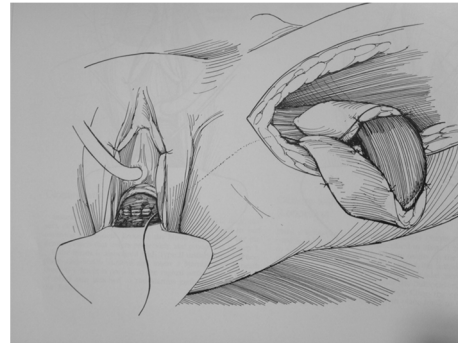


Labial fat pad provides additional blood supply, lymphatic drainage, surface for epithelialization, and prevents overlapping of the urinary and vaginal suture lines.

Peritoneal flap



Gracilis Myocutaneous Flap



Hinman 1998

Rectovaginal Fistula

- 5-10 % of those with Crohn's will develop RVF (lower in UC)
- Diverticulitis, Bartholin's, TB, Cryptoglandular abscess
- LAR for Cancer: 1-10%
- Prolapse surgery with or without mesh/graft
- Mechanical – Pessary, Sexual Practices, Trauma
- Cancer – up to 6% after radiation
- Principals suggest diversion if radiation, inflammation

Champagne BJ, Surg Slin N Am 90 (2010)
Venkatesh KS Dis Colon Rectum 1989
Tsang CBS, Surg Clinics N Am, 1997

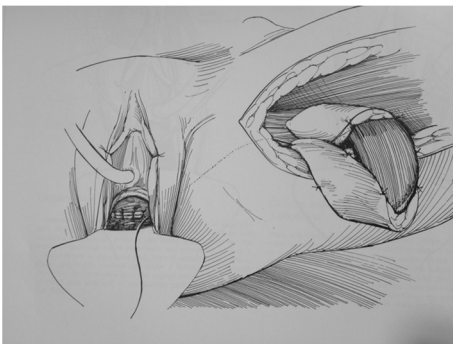
Treatment of recurrent rectovaginal/pouch-vaginal fistulas by gracilis muscle transposition – a single center experience

A. Troja*, P. Käse, N. El-Sourani, H.-R. Raab, D. Antolovic

Journal of Visceral Surgery (2013), <http://dx.doi.org/10.1016/j.jvisurg.2013.08.002>

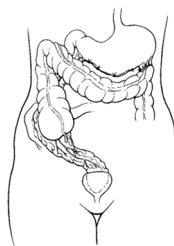
- 10 patients with recurrent GI-Vaginal Fistulas
 - 5 rectovaginal fistulas
 - 4 pouch-vaginal fistulas
 - 1 anovaginal fistula.
- Underlying disease:
 - 7 with Rectal cancer and XRT, 1 with Crohn's, 1 gynecologic surgery, 1 idiopathic
- Results:
 - Follow-up 8 to 60 months.
 - Recurrent rectovaginal fistula occurred in 4/10
 - Post-operative complications:
 - 1 perineal wound defect, 1 thigh hematoma.

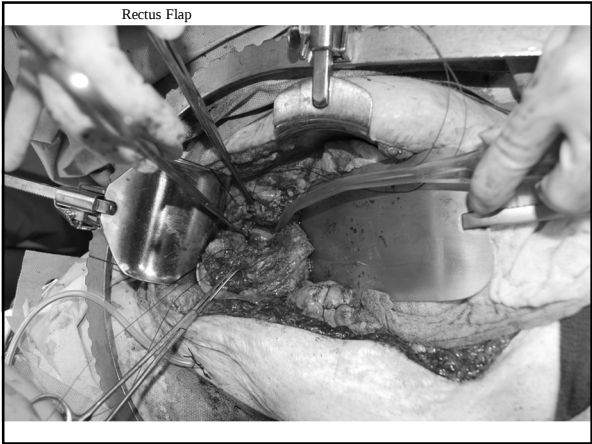
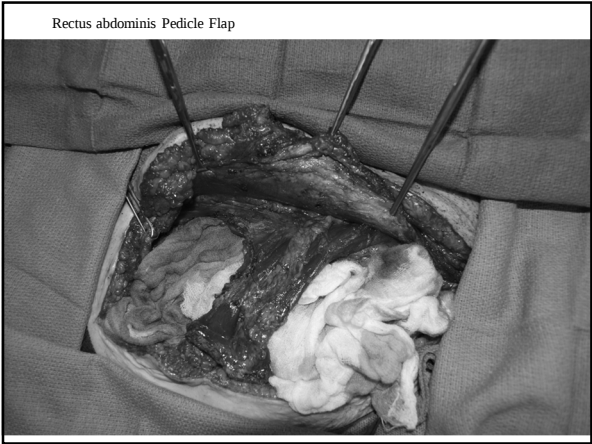
Gracilis Myocutaneous Flap



Hinman 1998

Omentum





Non Hysterectomy Fistula

- Tend to be complex
- Understanding the underlying disease process and the surgical principles for repair are key
- Workup of bladder function / ureters follows the same principles as in hysterectomy fistula

Original Research

Identifying Patients With Vesicovaginal Fistula at High Risk of Urinary Incontinence After Surgery

Angela M. Bengtson, PhD, Dawn Kopp, MD, Jennifer H. Tang, MD, Ennet Chikungu, MBS, Margaret Mayo, CNMT, and Jeffrey Wilkinson, MD

- 11 (3%) women had unsuccessful
- fistula closure. Of those with successful fistula closure
- (n5372), 85 (23%) experienced residual incontinence. A
- risk score cut point of 20 had sensitivity of 82% (95% confidence
- interval [CI] 72–89%) and specificity 63% (95% CI
- 57–69%) to potentially identify women with residual
- incontinence. In our population, the positive predictive
- value for a risk score cut point of 20 or higher was 43%
- (95% CI 36–51%) and the negative predictive value was
- 91% (95% CI 86–94%). Forty-eight percent of our study
- population had a risk score 20 or greater and, therefore,
- would have been identified for further intervention.

VOL. 128, NO. 5, NOVEMBER 2016 OBSTETRICS & GYNECOLOGY 945

Table 2. Bivariable and Multivariable Analyses to Develop a Risk Score to Identify Women at High Risk of Residual Urinary Incontinence

Preoperative Characteristic	Bivariable Analysis	
	OR (95% CI)	P
Age (yr)		
60 or younger	1.00	
Older than 60	3.20 (1.83–5.59)	<.01
No. of years with fistula		
5 or less	1.00	
6–20	2.02 (1.13–3.60)	.02
Greater than 20	3.16 (1.48–6.73)	<.01
HIV status		
HIV uninfected	1.00	
HIV infected	0.74 (0.27–2.02)	.56
BMI (kg/m ²)		
Less than 25.0	1.00	
25.0 or greater	0.98 (0.54–1.77)	.94
No. of prior fistula surgeries (at outside facility)		
0	1.00	
1 or greater	1.51 (0.84–2.71)	.17
Revised Gals classification		
Type 1	1.00	
Type 2	6.27 (3.54–10.49)	<.01
Type 3	11.44 (5.75–23.14)	<.01
Type 4	24.35 (9.02–65.72)	<.01
Gals vesicovaginal fistula size (cm)		
Less than 1.5	1.00	
1.5–3.0	2.08 (1.14–3.78)	.02
Greater than 3.0	3.19 (1.70–5.99)	<.01
Circumferential fistula		
No	1.00	
Yes	5.01 (3.07–8.16)	<.01
Vaginal scarring		
None or mild	1.00	
Moderate, severe, or obliterated	4.04 (2.35–6.95)	<.01
Bladder size		
Large (greater than 6 cm)	1.00	
Small or moderate (6 cm or less)	1.83 (1.11–3.03)	.02
Urethral length (cm)		
Greater than 1.5	1.00	
1.5 or less	5.07 (2.88–8.92)	<.01

OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; BMI, body mass index.

* ORs and P values estimated using logistic regression.

FEMALE UROLOGY

Which Surgical Technique Should be Preferred to Repair Benign, Primary Vesicovaginal Fistulas?

- The size of the fistulas ranged from 15 to 20 mm.
- The admission time was between 3 days and 21 years, and it was longer in less educated patients. The success
- rate was 96.4% (27/28) in the transabdominal transvesical group and 100% (25/25) in the transvaginal group ($P =$
- 1.00). The hospitalization period and complications were significantly reduced in the transvaginal group ($P = .00$
- and $P = .004$, respectively). No patients converted from a transvaginal to a transabdominal repair. There was only
- one recurrence in the transabdominal transvesical group. The patients were followed up for 1 year.
- Conclusion: Transvaginal repair of benign, primary VVFs is more advantageous than transabdominal transvesical
- repair. There was a significant decrease in the hospitalization period and complications rates using the transvaginal
- technique without tissue interposition.

954

ORIGINAL ARTICLE

Doctor! Will I be dry? Factors determining recurrence after vesicovaginal fistula repair

Atif Javed¹ Aziz Abdullah² Nuzhat Faruqi³ Sher Shah Syed⁴ Binat-ul-Mehdi⁵ Abdul Jabbar Pirzada⁶

- 640 patients
- Overall success in 558 (87.2%) cases.
- Multivariate analysis:
 - Multiplicity (9-fold recurrence risk)
 - Pre-operative size (10-fold recurrence risk for fistula >2cm compared to <1cm)
 - Secondary repair (5-fold risk)
 - Duration of the fistula (3-fold risk).

Interposition of flap and delayed reconstruction (between 6 weeks and 1 year) was related to successful surgical outcome. Age, parity, aetiology, route of repair and location of fistula were not significant ($p>0.05$ each) prognostic factors for recurrence.

- **Conclusion: Successful surgical repair of vesicovaginal fistula require careful evaluation of various factors, including** number, size, previous attempts to surgical repair and duration of fistula.

J Pak Med Assoc Vol. 65, No. 9, September 2015

590

Vol. 66, No. 5, May 2016 J Pak Med Assoc

ORIGINAL ARTICLE

Outcome of VVF repair without omental interposition

Fazal Wahab¹ Amir Nasir² Fazal Manan³

Results

There were 30 patients available, but 2(6.6%) were excluded. Among the remaining 28(93.3%) patients dehiscence was not noted in any patient, while only 4(14.3%) patients developed mild urinary tract infection. There were no intraoperative or postoperative deaths.



“Omental interposition is not essential for good healing”.

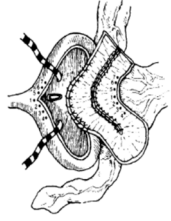
Tissue Loss

- In some cases pressure necrosis may destroy virtually the entire bladder, so that if the defect can be closed at all, the afflicted woman is left with a remarkably small (30 - 50 ml) bladder that compliance may be altered by the extensive fibrotic changes that often take place.
- To date there have been few urodynamic studies reported on patients who have undergone successful fistula closure

Schleicher DJ, Ojenghede OHA. International Urogynecology Journal 1993;4:262-5.
Carey MP, Goh JT, Fynes MM, Murray CJ. Am J Obstet Gynecol. 2002 May;186(5):948-53.

Compliance/Capacity

- Decision-making regarding integration of augmentation into the repair of the fistula
- Diversion – Catheterizable +/- cystectomy



Tabakov ID, Slavchev BN. J Urol 171, 272–274, January 2004

Bladder and Urethral Diverticula

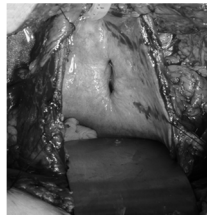


Eric S. Rovner, M.D.
Professor of Urology
Medical University of South Carolina

No Relevant Disclosures

Bladder Diverticula

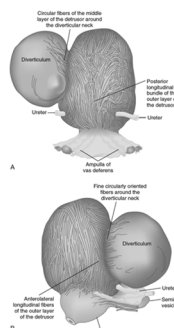
- Agenda:
 - Etiology and Pathophysiology
 - Diagnosis and evaluation
 - Management



Pathophysiology and Etiology

- Classification
 - Congenital (non-neurogenic, non-PBS/PUV, etc.)
 - Usually solitary
 - Smooth walled bladder
 - Males (usually <10 y.o.)
 - Paraureteric (weakness in detrusor adjacent to ureter)
 - Associated syndromes: Menkes, Williams, Ehlers-Danlos, etc
 - Acquired (“secondary”)
 - BOO/NGB (“Hutch”: paraureteric)/Post surgical
 - Often multiple, male
 - Associated with saccules, cellulites, etc.

Histology/Anatomy



- Mucosa, +/- lamina propria, adventitia, capsule
- Few if any detrusor fibers
- No contractile properties, empties poorly

Rovner, E.S.: Bladder and Female Urethral Diverticula.
In Wein,et al. (eds): Campbell's Urology, 10th edition,
Elsevier, p. 2263, 2012

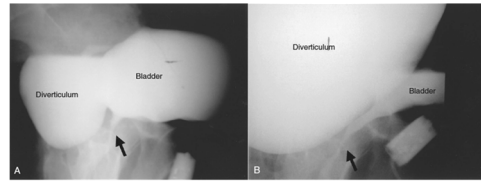
Diagnosis

- Often asymptomatic
 - non-specific presentation
- Incidental finding
 - Found on evaluation for other sx, sign
 - Hematuria, UTI, LUTS/BOO, etc.
 - Imaging “incidental” finding

Evaluation

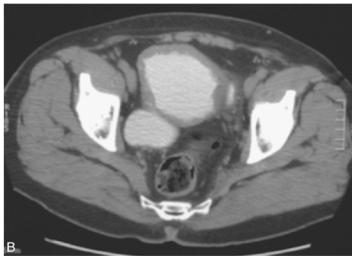
- History, PE, UA, cytology
- Radiographic: VCUG, CT, MRI, etc
- Cystoscopy
- Urodynamics

VCUG



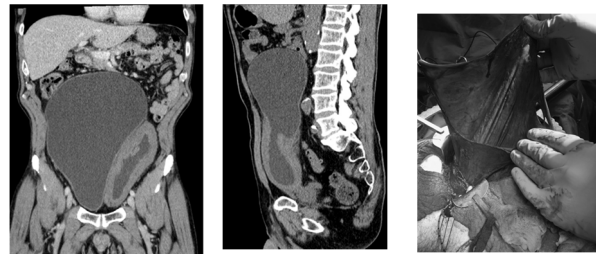
Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, A.J., Kavoussi, L., Novick, A., Partin, A., and Peters, C. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2264, 2012

CT Cystogram



Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2265, 2012

Large Bladder Diverticulum

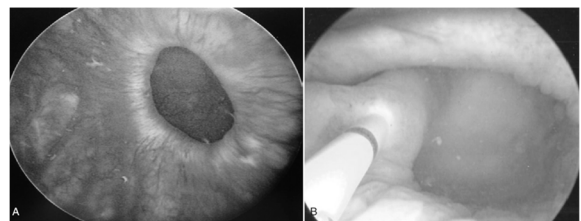


IVP



Medial deviation
of ureter

Cystoscopy



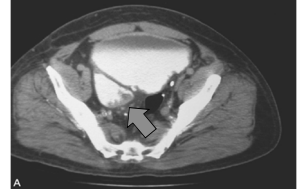
Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2266, 2012

Urodynamics and Bladder Diverticula

- Acquired BD often associated with BOO/NGB
- Necessary to identify the underlying abnormality
 - Beware
 - BD may act as “pressure sink” underestimating contractility
 - Artificially elevated PVR (role for VUDS)
- Treat BD AND underlying abnormality
 - Sequential or concomitantly
 - If BOO treated and BD empties, then ?need for surgery

Indications for intervention

- Natural history unknown
 - ? Increased risk for malignancy (stasis)
- Symptoms/Signs attributable to tic
 - UTI
 - Abdominal/Pelvic discomfort
 - LUTS
 - Malignancy
 - Hydronephrosis
 - Other

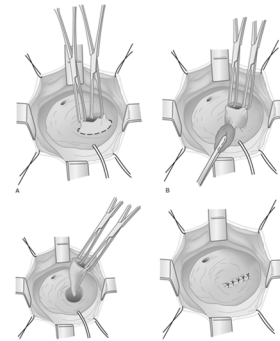


Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2265, 2012

Management

- If Asymptomatic:
 - Observation/expectant management
 - Surveillance (malignancy risk??)
- If Symptomatic:
 - CIC (?)
 - Endoscopic management
 - Surgical management
 - Transabdominal
 - Open vs. minimally invasive
 - Extravesical vs. Intravesical vs. combined

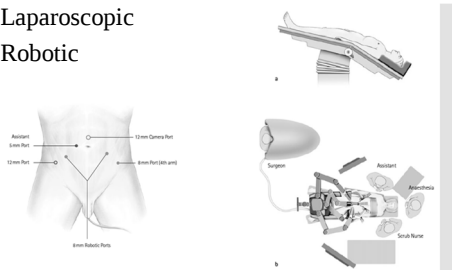
Transvesical



Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2271, 2012

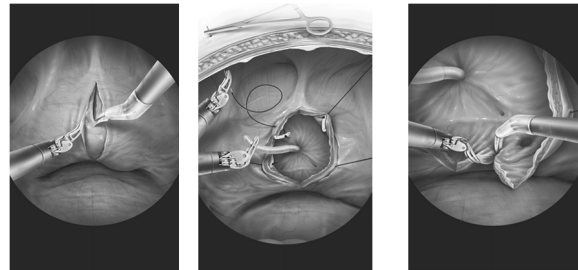
Minimally Invasive

- Laparoscopic
- Robotic



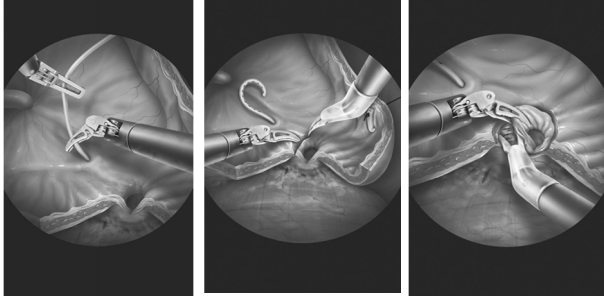
Thuroff et al: Surgery Illustrated – Surgical Atlas Robot-assisted laparoscopic bladder diverticulectomy BJUI 110: 1820–1836 2012

Robotic Bladder Diverticulectomy (transperitoneal)



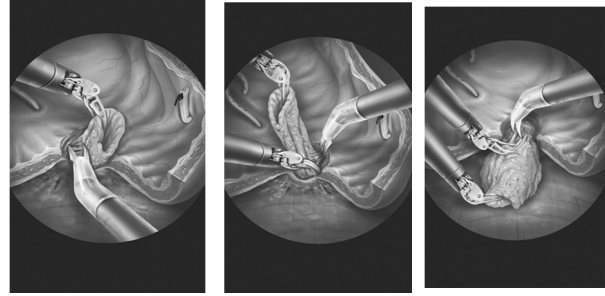
Thuroff et al: Surgery Illustrated – Surgical Atlas Robot-assisted laparoscopic bladder diverticulectomy BJUI 110: 1820–1836 2012

Robotic Bladder Diverticulectomy



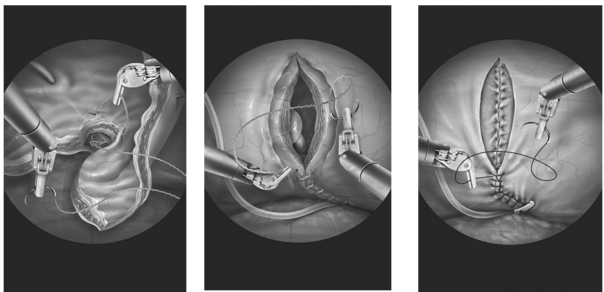
Thuroff et al: Surgery Illustrated – Surgical Atlas Robot-assisted laparoscopic bladder diverticulectomy BJUI 110: 1820–1836 2012

Robotic Bladder Diverticulectomy



Thuroff et al: Surgery Illustrated – Surgical Atlas Robot-assisted laparoscopic bladder diverticulectomy BJUI 110: 1820–1836 2012

Robotic Bladder Diverticulectomy



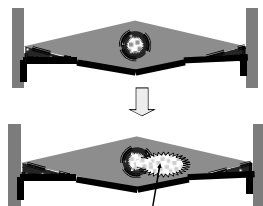
Thuroff et al: Surgery Illustrated – Surgical Atlas Robot-assisted laparoscopic bladder diverticulectomy BJUI 110: 1820–1836 2012

Female Urethral Diverticula

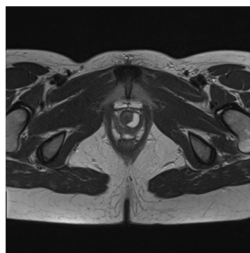
- Agenda:
 - Diagnosis
 - Evaluation
 - Management



Urethral Diverticulum



Diverticulum forms within the urethropelvic ligament, usually lined by epithelium



Reuser, E.S.: Bladder and Female Urethral Diverticula. In: Wein et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2275, 2012

UD: Prevalence

“.....found in direct proportion to the avidity with which it is sought”*

- Davis, Te Linde, et al, JU 1958
 - @ Johns Hopkins:
 - 1894-1955: 9 UD
 - 1955-1956: 50 UD (development of PPU)

*Moore, JU 1952

Urethral Diverticula: Prevalence

Overall: 0.6 – 4.7% of females (????)

- Depends on series
 - Primary vs. Tertiary care, GU vs. GYN, sx's, etc.
 - Autopsy: 3/500
 - ASx patients: 3/300 on PPU***
 - 4.7% of ASx females screened for UD on admission for OB/GYN problems
 - Asymptomatic vs. symptomatic patients
 - Up to 40% of patients with LUTS suggestive of UD have UD**
 - 4-20% of patients with UD are ASx at presentation
- Underdiagnosed?
 - Non-communicating UD*

*Daneshgari F et al. J. Urol. 1999

**Stewart et al, BJU, 1981

***Andersen, et al, J Urol 1967

Prevalence exaggerated ??

- Recent study on UD incidence
 - Records of Rochester Epidemiology Project
 - Olmstead county 1980-2011
 - 26 new cases (Mayo: 142 cases)
 - Annual incidence = 17.9/1,000,000

El-Nashar SA et al.: IUJ, 2013

UD: Etiology (congenital vs. acquired)

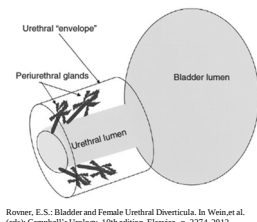
-Congenital

Rare reported cases in peds

-Acquired

Paraurethral Glands (*prostatic analogue*)

- Drain into distal 1/3 of urethra
 - Most distal are Skenes
- Largest and highest concentration of glands are located laterally and dorsolaterally
 - Secretory, columnar epithelium
 - Ductal/periductal inflammation common



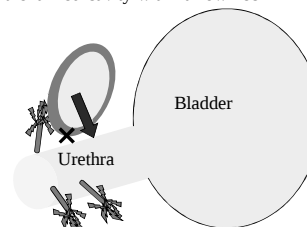
Rovner, E.S.: Bladder and Female Urethral Diverticula. In: Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2274, 2012

Urethral Diverticula: Pathophysiology*

- Obstruction of paraurethral ducts/glands
 -dilation
- Abscess formation (?)
- Rupture back into urethral lumen
- Residual epithelialized cavity with narrow neck

Evidence for UD origin in Paraurethral glands

- UD located usually in mid 1/3 of urethra
 - Variable size, shape and extension toward BN*
- Ostia located postero-laterally (dorso-laterally)
- 10% bilateral
- Epithelium variable: columnar, transitional, cuboidal, or absent



*Routh, 1890

UD: Risk Factors/Associations

Historically:

1. Trauma: childbirth, multiparity
 - but up to 1/3 occur in nullips*
2. Race: african americans up to 6 fold incidence
 - ?but population bias at those reporting centers*
3. Gonococcal infection
 - but most culture out e. coli in urine*

Urethral Diverticula: Diagnosis (often missed)

History:

- often non-specific presentation over years
- irritative voiding symptoms, pain, UTI
- (3 "D's": Dysuria, Dyspareunia, *post-void* Dribbling)

Physical examination:

- tender anterior vaginal wall mass with urethral discharge upon palpation and stripping of anterior vaginal wall

Imaging

Endoscopy

+/- Urodynamics

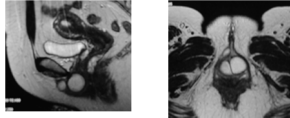
Difficult Diagnosis

• Radiographic Diagnosis*

- 65% VCUG (30)
- 11% Double balloon PPU (5)
- 15% MRI/Ultrasound (7)
- 9% *incidentally found during surgery (4)*

*Romanzi, Blaivas: JU 164:428, 2000

BEWARE: prior periurethral bulking agents



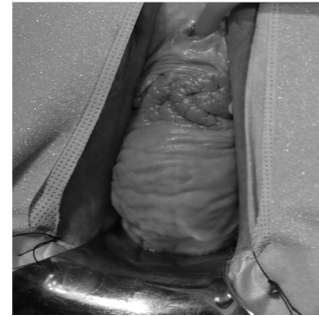
Periurethral Masses: Differential Dx

- Retrospective review
- 78 consecutive patients with periurethral masses
 - 84.6% UD
 - 3 with occult cancer
 - 4.1% vaginal leiomyoma
 - 3.8% vaginal cyst
 - 2.6% ectopic ureter
 - 3.8% other: Nabothian cyst, Sq. cell Ca, infected granuloma

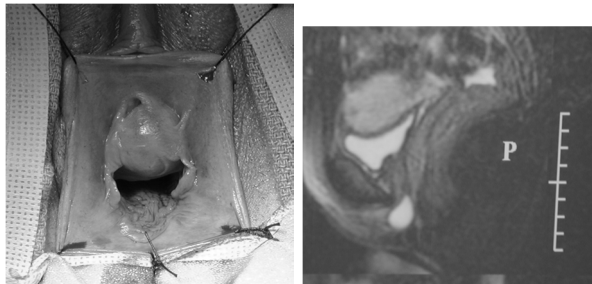
Flisser, A., Blaivas, J. et al, JU



Anterior vaginal wall prolapse

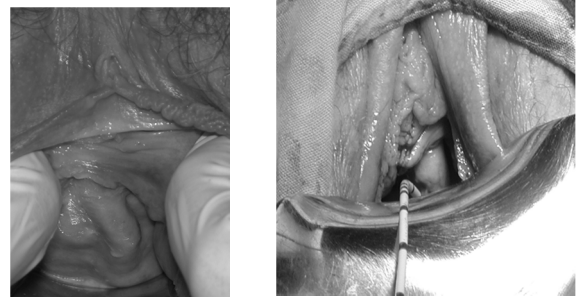


Skene's Gland Cyst



Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2282, 2012

Ectopic Ureter



Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2282, 2012

Vaginal leiomyoma

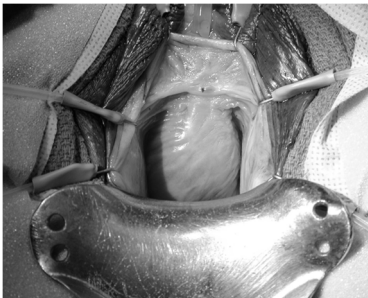


Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2282, 2012

Vaginal Leiomyoma



Urethral Diverticulum

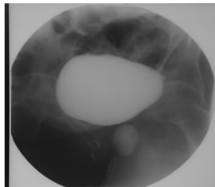


Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2278, 2012

UD: complicating/co-existent conditions

- Tumors (<100 cases reported)
 - Malignant:
 - AdenoCa: 46%
 - TCCa: 38%
 - Sq. Cell Ca: 12%
 - Benign: nephrogenic adenoma, endometriosis
- Incontinence: up to 57%
 - Differentiate from post-void dribbling
 - Role for VUDS
 - If true, bothersome SUI: Consider aPVS (NOT MUS)
- UTI's (may or may not resolve)
- Pelvic pain/dyspareunia (may or may not resolve)
- Stones (up to 10%)

66 y.o. with dyspareunia and UTI's



Urethral Diverticula (Imaging)

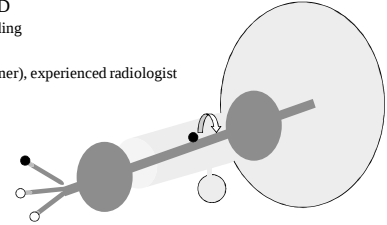
- Why image ?
 - Confirm clinical diagnosis:
 - Skene's gland cyst, leiomyoma, prolapse, etc.
 - Anatomy
 - location
 - sphincter/bladder neck
 - size/complexity/urethral involvement
 - ostia

Urethral Diverticula

- PPU (Double balloon)
- VCUG
- Transvaginal Ultrasound
 - operator dependent
 - images lack precise “surgical anatomy”
- **MRI**

PPU

- Positive Pressure Urethrography (*Davis and Cian 1956*)
- Double balloon technique
 - Highly specific for UD
 - not dependent on voiding
 - Requires
 - special catheter (Trattner), experienced radiologist
 - Invasive

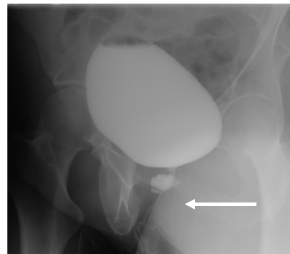


Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2279, 2012

VCUG

- Invasive, painful
- must void to image UD
- ostia must be patent to image UD
- poor stream will underestimate size, loculations(?)
- Utility
 - Readily available
 - Inexpensive

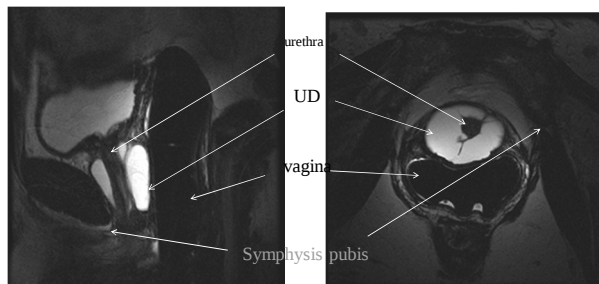
53 y.o. with incontinence s/p urethral diverticulectomy elsewhere



Urethral Diverticula and MRI

- Surface coil
 - Hricak, et. al., Radiology, 178:527, 1991 (9 patients)
 - Kim, et. al., AJR, 161:809, 1993 (16 patients)
 - Neitlich, et. al., J. Urol., 159:408, 1998 (6 patients)
- Endoluminal coil (endovaginal, endorectal)
 - Siegelman, et. al., Radiographics, 17:349, 1997
 - Blander, Rovner, et. al., Urology, 53:818, 1999 (case report)
 - Blander, Rovner, et al, Urology 57: 660, 2001 (27 patients)

eMRI



Morphology of Urethral Diverticula

UD

Saddlebag UD

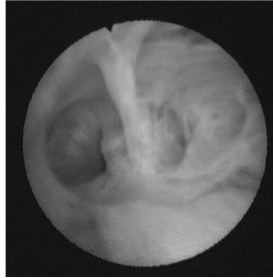
Circumferential UD



UD

Endoscopy

- Flexible cystoscopy
- Rigid with “female sheath”
- Assess:
 - Ostia (number, location, etc.)
 - Sphincter
 - bladder neck competence, etc.



Urodynamics/videourodynamics

- Consider if:
 - Significant LUTS/UI
 - Differentiate between SUI and post void dribbling
 - Elevated PVR: BOO vs. detrusor underactivity

Management of UD

- Non-operative
 - Watchful waiting (Asymptomatic)
 - Antibiotic prophylaxis (if UTI)
 - Digital stripping of anterior vaginal wall
- Operative
 - Endoscopic management
 - Spence-Duckett
 - Marsupialization
 - Excision and reconstruction (+/- sling)

Excision of Urethral Diverticula

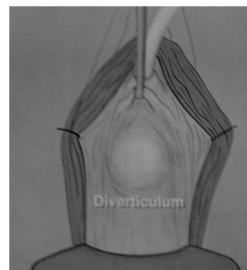
Principles

- preservation of the periurethral fascia
 - closure of dead space
 - multi-layered closure
- identify and excise the neck or ostia
- remove epithelialized sac
- preserve or create continence

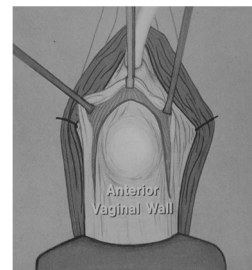
Operative Preparation

- Proper consent:
 - Recurrence of symptoms/UD
 - Review complications (fistula, SUI, etc.)
 - +/- episiotomy, Martius flap
- Urine culture (antibiotics)
- Lone Star retractor, weighted speculum
- Loupes, headlight

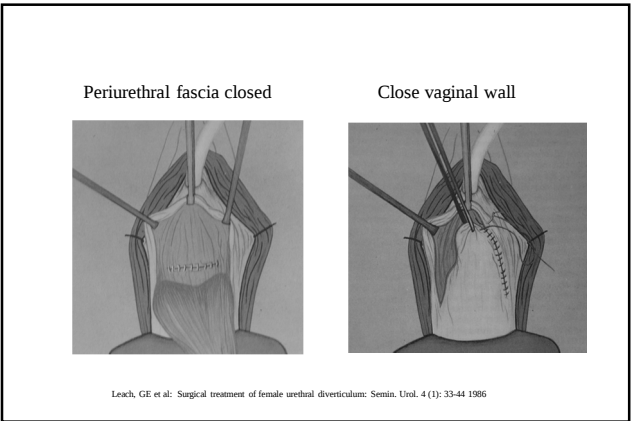
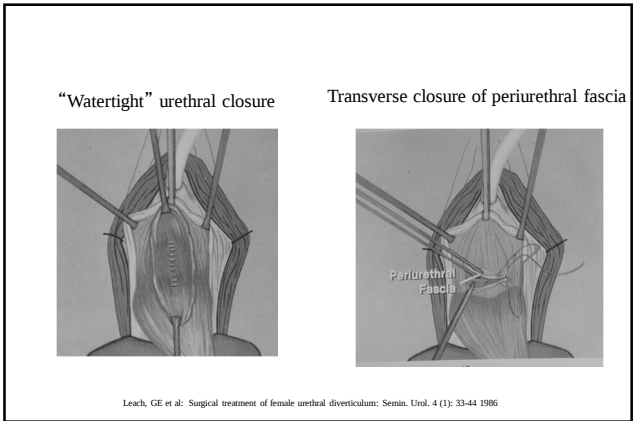
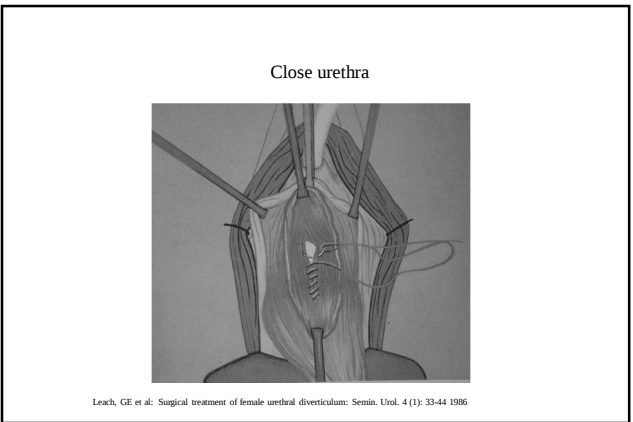
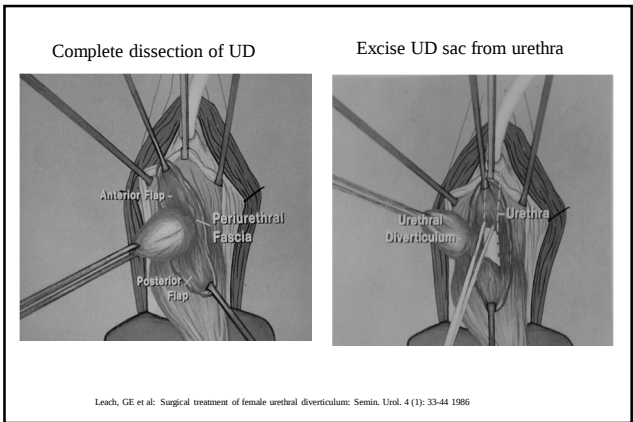
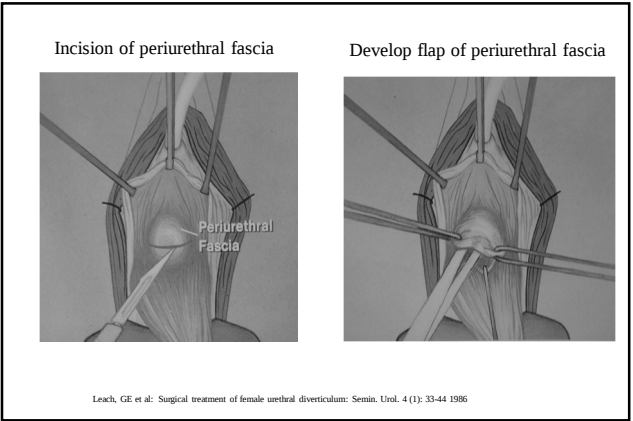
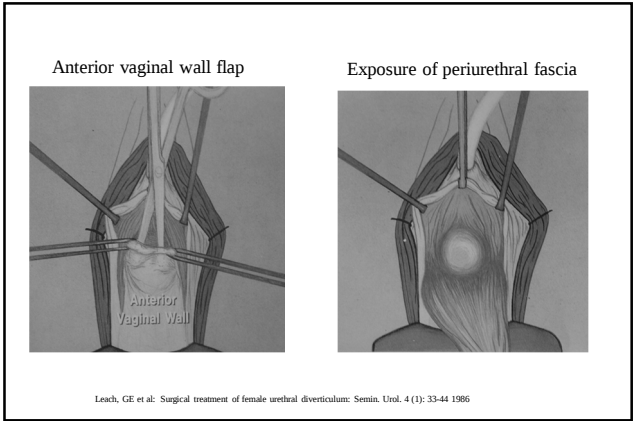
Exposure



Inverted “U” incision



Leach, GE et al: Surgical treatment of female urethral diverticulum: Semin. Urol. 4 (1): 33-44 1986



Complications of Transvaginal Urethral Diverticulectomy (UD)

Complication (% Range of Reported Incidence)

Urinary incontinence (1.7%-16.1%)

Urethrovaginal fistula (0.9%-8.3%)

Urethral stricture (0%-5.2%)

Recurrent UD (1%-25%)

Recurrent urinary tract infection (0%-31.3%)

Other:

Hypospadias/distal urethral necrosis

Bladder or ureteral injury

Vaginal scarring or narrowing: dyspareunia, etc.

Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein, et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2277, 2012

Summary:

Bladder and Urethral diverticula

-Can be difficult diagnosis

-Anatomy variable

BUT: anatomic problem=anatomic solution

-Primary treatment:

surgical excision and reconstruction



Non-Muscle Invasive Bladder Cancer

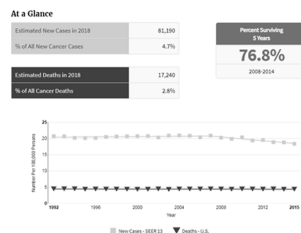
Angela B. Smith, MD, MS, FACS
Associate Professor
Department of Urology
University of North Carolina
Lineberger Comprehensive Cancer Center

Disclosures

- AHRQ K08 (research funding)
- PCORI (research funding)
- Photocure consultant (for consensus guidelines)

Bladder Cancer Statistics

- Incidence: ~81,190
 - » 75% NMIBC
 - » 20% MIBC
 - » 5% metastatic
- Prevalence: ~675,000
- 17,240 deaths annually



3

Epidemiology

- Median age 72 years
- Male:Female 3:1
 - » 4th most common cancer in US men
 - » 12th most common cancer in US women
- Racial predominance:
 - » Caucasians > African Americans > Hispanics > Asians
 - » Higher death rate among women and African Americans

Risk Factors

- Cigarette smoking
 - » Risk increases 2-6 times
- Pelvic radiation
 - » Prostate, rectal, cervical cancers
- Drugs
 - » Cyclophosphamide, ifosfamide, phenacetin
- Chronic cystitis
 - » Schistosoma hematobium (bilharziasis)
- Environmental exposure
 - » Aluminum, dyes, paint, textiles, petroleum, rubber
- Genetics
- Miscellaneous
 - » Arsenic, Balkan nephropathy (Aristolochia species)

Genetics

- <10% cases have family history
- Relative risk increases 2-fold with FH but non-hereditary
- Lynch Syndrome II
 - » Defect in DNA mismatch repair
 - » Rare familial syndrome
 - » Predisposes to bladder and UTUC
- Polymorphisms in detoxification mechanisms contribute to higher susceptibility to environmental carcinogens
 - » Among smokers
 - » Glutathione-S-transferase M1 null genotype → higher risk

Prevention of bladder cancer

- Eliminate initiating risk factors

Smoking (33-50%)
Occupational exposure (25-27%)
Radiation
Chemotherapeutic agents
Catheters, foreign bodies

- Suppressing promotion in initiated cells

Diet
Vitamins
Oral agents

Chemoprevention

- High dose antioxidant vitamins have unclear benefit
 - » Vitamins A, B1, B2, B3, B5, B6, B12, C, D, E, folate, zinc
 - » May have a role for LG UC after BCG
 - » Potential hepatotoxicity of high doses of Vitamin A
- Fruit and vegetables – **DECREASED** risk
- Fat and cholesterol – **INCREASED** risk
- Non-chlorinated water > 6 cups/day – **DECREASED** risk

Screening



- Potential benefits of screening
 - » Easily performed
 - » Early detection
 - » Rarely indolent (found on autopsy)
- Screening – not recommended by USPSTF (2011)
 - » Incidence 21/100,000 (0.02%)
 - » Not specific; increase burden with false +
 - » Heterogeneous nature of bladder cancer
- Enrich the screened population
 - » Smokers?
- Better screening tools beyond dipstick UA

Signs and Symptoms

- Intermittent gross painless hematuria (80%)
- Irritative voiding (20%)
- Mucosuria
- Additional signs/symptoms rare
 - » Usually related to advanced cancer
 - » Not noted in NMIBC
- Incidental diagnosis (imaging)



2016 AUA/SUO Guidelines for NMIBC

2007 Panel members

M.Craig Hall, M.D., Chair
Sam S. Chang, M.D.
Guido Dalbagni, M.D.
Raj S. Pruthi, M.D.
Paul F. Schellhammer, M.D.
John D. Seigne, M.D.
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2016 Panel members

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Jim McKiernan, M.D., Vice Chair
Steve Boorjian, M.D.
Peter Clark, M.D.
Sia Danshmand, M.D.
Badri Konety, M.D.
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Diane Quale, Patient Advocate
Chad Ritch, M.D.
John D. Seigne, M.D.
Eila C. Skinner, M.D.
Norm Smith, M.D.

NMIBC DIAGNOSIS

Evaluation

- Imaging of Upper Tracts
 - » CT urogram, MRI, retrograde pyelogram, IVP
 - » Prior to TURBT preferred
- Cystoscopic inspection of the bladder
- Transurethral Resection of Bladder Tumor (TURBT)
- Additional considerations
 - » Enhanced cystoscopy (when available)
 - » Random biopsies
 - » Upper tract washes
 - » Prostate urethral biopsies
- Urinary Cytology

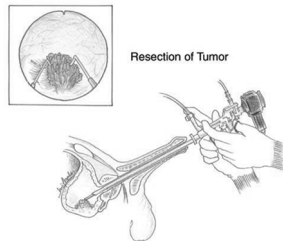


CT Urogram



TURBT

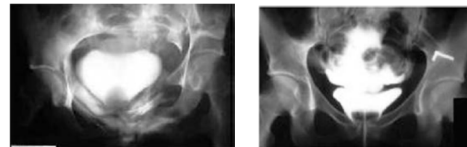
“Focal”
 “Targeted”
 “Personalized”
 “Single-port”
 “Natural orifice”
 “Scope”
 “No scalpel” technique
 “Minimally invasive”



Slide courtesy of S. Chang

Complications of TURBT

- Urinary tract infection
- Bleeding (early or delayed)
- Bladder perforation
 - » Associated with the obturator reflex
 - » Distinguish extra from intraperitoneal (intraop cystogram)
 - EP can be managed conservatively
 - IP (particularly if large) should be repaired



TURBT: Experience Makes a Difference

- When compared to experienced surgeons, lesser experienced surgeons
 - » more likely to leave residual tumor (OR 7.3)
 - » more likely to lack muscle in the specimen (OR 8.5)
 - When detrusor muscle **present** - residual tumor rate **20%**
 - BUT when detrusor muscle was **absent** - residual tumor rate **51%**

Huang J et al, Urol Int 89 (2012)

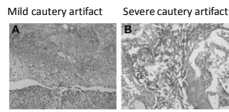
Monopolar vs Bipolar Electrocautery

- Puppo et al assessed the safety of bipolar TURBT in 480 consecutive patients
 - » 2% rate of obturator nerve reflex
 - » 0.8% blood transfusion rate
 - » no cases of transurethral resection syndrome
 - » no thermal skin lesions

Puppo P et al, J Endourol, 23 (2009)

Monopolar vs Bipolar Electrocautery

- Randomized, single center trial examined 147 patients and found
 - No difference** in:
 - Bleeding
 - Obturator reflex
 - Operative time
 - Hyponatremia
 - Complications
 - The only advantage was decreased cautery artifact with bipolar



Venkatramani et al, J Urol, June 2014

Cystoscopy and Biopsy

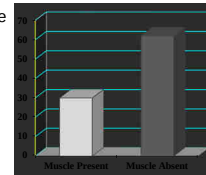
- Cold cup excisional biopsy with fulguration is acceptable for small papillary tumors
- Office laser or fulguration (without biopsy) could be considered for established low-grade small papillary lesions
 - » Studies ongoing to determine safety of active surveillance
- Tumor in a diverticulum
 - » Ta disease can be safely removed if technically feasible
 - » T1 disease (particularly high grade) may be understaged
 - Consider partial cystectomy/diverticulectomy if isolated
 - Consider random bladder biopsies of diverticular rim to assure cancer limited to diverticula

Importance of Re-TURBT

- Incomplete resection is likely a significant contributing factor to early recurrences, as tumors have been noted at the first follow-up cystoscopic evaluation in up to 45% of patients*
- Repeat resection should be:
 - » Performed after an incomplete initial resection if feasible
 - » Considered for those with high risk HGTA tumors
 - » Performed for those with HGT1 disease

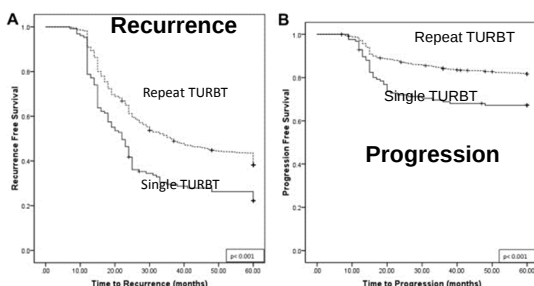
Why re-resect T1 disease?

- Understaging in about 30%
 - Greater (up to 50%) with no muscle in the specimen
- Patients w/ residual T1 (after presumed complete resection) have up to 80% chance of progression



Cookson MS, et al. J Urol 2001;166:490

Re-TURBT Decreases Recurrence and Progression



Sfakianos JP et al, J Urology, February 2014

Can re-TUR of T1 tumors select patients for immediate cystectomy?

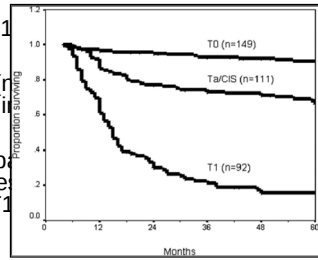
- 352 T1 tumors evaluated by restaging TUR
- 58% (n = 203) had residual tumor on restaging including 92 (26%) with residual T1
- 82% patients with residual T1 cancer progressed to T2 compared to 19% with no or non-T1 tumor on re-TUR

5 year progression probability

Herr HW, et al. J Urol 2007;177(1):75-79

Can re-TUR of T1 tumors select patients for immediate cystectomy?

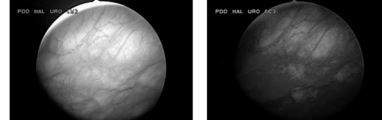
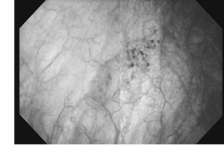
- 352 T1 tumors resected by TUR
- 58% (n=204) re-staged
- 82% progression probability with no or non-T1



Herr HW, et al. J Urol 2007;177(1):75-79

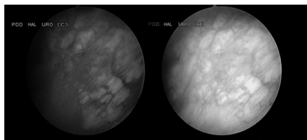
Enhanced Cystoscopy

- Blue Light
 - » 5-ALA
 - » Cysview/Hexvix
- Narrow Band Imaging



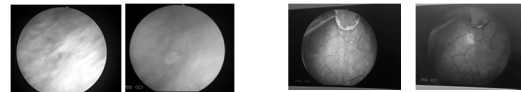
Fluorescence Cystoscopy

- Hexaminolevulinate or precursor 5-ALA – causes porphyrins to accumulate in tumor cells
- Porphyrins emit red color when exposed to blue light
- Instill 50cc into empty bladder and empty after 1 hour
- Perform white and blue (380-450nm) light cysto within 1 hour
- Use in OR with rigid cystoscopy (although flexible also recently approved)



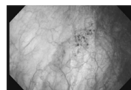
Blue Light Cystoscopy

- A clinician should offer blue light cystoscopy:
 - » At the time of TURBT, to increase detection and decrease recurrence
 - Detection increased 20-30% papillary; 30-40% CIS
 - 12 month recurrence is absolute 10% less with BL
 - » In the presence of positive cytology with negative white light standard cystoscopy



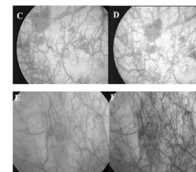
Narrow Band Imaging

- Filters the white light into specific light wavelengths that penetrate only surface of human tissue and absorbed by hemoglobin:
 - » 415 (blue)
 - » 540 (green)
- Capitalizes on peak absorption of hemoglobin
- Accentuates vascular architecture of bladder tumors (compared to normal urothelium)
- Does not require instillation agent
- Avoids time delay and cost of agent



Narrow Band Imaging

- A clinician may consider use of Narrow Band Imaging (NBI) to:
 - » increase detection and decrease recurrence
 - » Similar detection rates as BL but fewer studies; no randomized comparison



- superficial capillary network (brown)
- deeper vessel visibility: vessels are greenish-blue (cyan)

Cauberg EC et al. Urol 76: 658, 2010

Random Biopsies

APPROPRIATE

- Cytology is positive yet no tumor is present
- Follow-up of prior CIS after treatment
- When contemplating partial cystectomy or bladder sparing approaches to rule out CIS

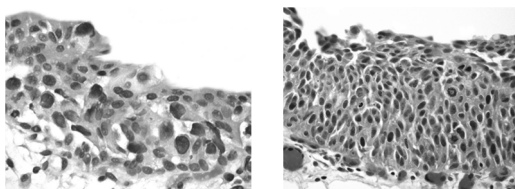
NOT APPROPRIATE

- Normal mucosa and tumor appears papillary, non-invasive with negative cytology

Localizing Source of Positive Cytology

- Bladder (random biopsy and enhanced cysto)
- Upper tracts (selective cytology and imaging)
 - » Ureteroscopy if equivocal
- Prostatic urethra
 - » Biopsy 5 and 7 o'clock, TURP
- GYN source if workup completely negative
- If full workup negative, >80% likelihood cancer cells still coming from bladder

Evaluate the Prostatic Urethra



- **Up to 40%** of patients may have involvement of prostatic urethra in patients with invasive disease and can be easily missed
- Important **predictor of invasive disease**
- TUR biopsies at **5 and 7 o'clock** adjacent to veru can help detect CIS

Wood D et al. J Urol. 1989; Huguet J, et al. Eur Urol. 2005;48:53-59

Urine Markers

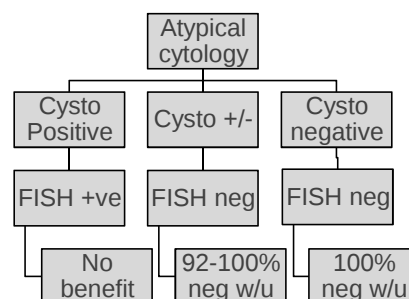
- Commercial urine based markers for bladder cancer detection and/or surveillance
 - » Cytology
 - » BTA *stat* and TRAK
 - » NMP22 and BladderChek
 - » ImmunoCyt
 - » UroVysion FISH
 - » CertNDx
 - » Cx Bladder
- No study has evaluated effectiveness of urinary biomarkers to decrease mortality or improve outcomes compared with standard diagnostic methods

Urine Markers

- *Given uncertainty in sensitivity these test CANNOT replace cystoscopy*
- *In general, lower specificity than cytology*

9. In surveillance, should **not** use urinary biomarkers in place of cystoscopy. (Strong Recommendation; Evidence Strength: Grade B)
10. History of low-risk cancer and a normal cystoscopy, should **not** routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)
11. May use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

Atypical cytology and FISH



Schlomm BJ et al. J. Urol. 2010

FISH and response to BCG

	Recurrence if post BCG FISH		% ≥T2
	Positive	Negative	
Kipp	100%	52%	58%
Whitson	89%	26%	
Mengual	52%	25%	10%
Savic	76%	26%	

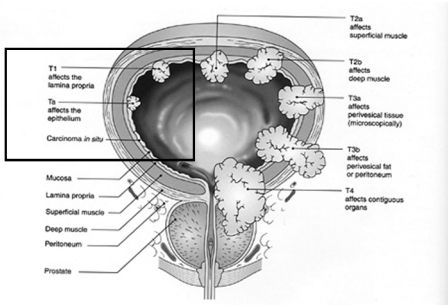
- Post BCG FISH predicts for recurrence and progression
- FISH useful if post BCG cytology equivocal

Whitson J, et al. BJU Int. 2009; Kipp et al. J. Urol. 2005
Mengual et al. Eur. Urol. 2007; Savic et al. Int. J. Cancer. 2009

Cytology

- A normal result cannot rule out cancer
- 95% accurate if unequivocally positive for HG dysplastic cells
- False positives more common for "papillary clusters" especially with stones or instrumentation
- Ileal conduit or neobladder cytology accurate if positive but pathologist needs to know it is from a bowel segment
- Also difficult to evaluate cytology after radiation or intravesical chemotherapy (bottom line- communicate to your cytopathologist)

Non-Muscle Invasive Bladder Cancer (NMIBC)

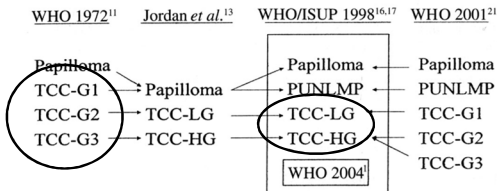


Staging of primary tumors (T) in bladder cancer	
TX	Primary tumor cannot be assessed
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (CIS)
T1	Tumor invades lamina propria
T2	Tumor invades muscularis propria
T2a	Tumor invades superficial muscularis propria (inner half)
T2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat
T3a	Tumor invades perivesical tissue/fat microscopically
T3b	Tumor invades perivesical tissue/fat macroscopically (extravesical mass)
T4	Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a	Tumor invades adjacent organs (uterus, ovaries, prostate stoma)
T4b	Tumor invades pelvic wall and/or abdominal wall

Staging

American Joint Committee on Cancer (AJCC), also known as the Tumor-Node-Metastases (TNM) classification. Clinical stage reflects the histologic findings at TURBT; the clinician's physical exam, including bimanual exam under anesthesia; and findings on radiologic imaging.
Edge 2010

World Health Organization (WHO) Classification of Urothelial Neoplasms



Reuter V. Urology 2006; 67:3A 11-18

Grading

2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia ¹⁶
Hyperplasia (flat and papillary)
Reactive atypia
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-muscle invasive low-grade papillary urothelial carcinoma
Non-muscle invasive high-grade papillary urothelial carcinoma

Risk Stratification

- EORTC and CUETO risk calculators
- Limited by lack of applicability to current populations
 - » Few patients received BCG maintenance, re-staging TURBT, or post-operative mitomycin C.
- EORTC uses 1973 WHO grading system
- Does not incorporate prior use of BCG or treatment
- C-index (0.5 = coin flip; higher is better)
 - » EORTC = 0.66 / 0.75
 - » CUETO = 0.64 / 0.70

EORTC Risk Tables for Stage Ta T1 Bladder Cancer

Prior Recurrence Rate
☐ Primary
☐ Recurrent <= 1 per year
☐ Recurrent > 1 per year

Number of Tumors
☐ 1
☐ 2 to 7
☐ 8 or more

Tumor Diameter
☐ < 3 cm
☐ >= 3 cm

T Category
☐ Ta
☐ T1

Grade (WHO 1973)
☐ G1
☐ G2
☐ G3

Concomitant CIS
☐ No
☐ Yes

Calculate Probabilities Clear Exit

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.38	0.51	0.56	0.59	0.62
Probability of Progression	0.01	0.03	0.04	0.05	0.06

Reference: Sylvester R.J. van der Meijden APM, Oosterlinck W, Witjes JA, Bouffoux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

Programmed by Richard Sylvester, EORTC Data Center, 63 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

EORTC Risk Tables for Stage Ta T1 Bladder Cancer

Prior Recurrence Rate
☐ Primary
☐ Recurrent <= 1 per year
☐ Recurrent > 1 per year

T Category
☐ Ta
☐ T1

Calculate Probabilities

Probability of Recurrence
 Probability of Progression

Reference: Sylvester R.J. van der Meijden APM, Oosterlinck W, Witjes JA, Bouffoux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

Programmed by Richard Sylvester, EORTC Data Center, 63 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

AUA/SUO Risk Stratification

TABLE 4: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer		
Low Risk	Intermediate Risk	High Risk
LG ^a solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP ^b	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG ^c Ta, ≤ 3cm	Any CIS
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LV ^d
		Any HG prostatic urethral involvement

^aLG = low grade; ^bPUNLMP = Papillary urothelial neoplasm of low malignant potential; ^cHG = high grade; ^dLV = lymphovascular invasion;

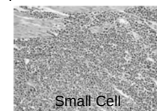
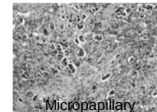
- At the time of each occurrence/recurrence, assign a clinical stage and classify a patient accordingly as "low-," "intermediate-," or "high-risk." (Moderate Recommendation; Evidence Strength: Grade C)

Histology - Conventional

- 90-95% urothelial carcinoma
- 5% squamous cell carcinoma
- 0.5-2% adenocarcinoma
 - » Usually arise from urachus or trigone
 - » Can be prevalent among patients with bladder exstrophy
 - » Many have history of long-term inflammation/infection
 - » Non-urachal adenocarcinoma should undergo colonoscopy
 - Distinguish from extension of colorectal primary

Variant Histology

- At TURBT, 86% (vs. 53%) with variant histology present with MIBC
- At cystectomy, 64% (vs. 34%) with variant histology with pT3-T4
- Micropapillary
 - » Unusual variant of UC but particularly resistant to BCG
 - » Early cystectomy preferred
- Plasmacytoid and Nested variants
 - » Aggressive
 - » Cystectomy preferred
- Small cell (neuroendocrine)
 - » Stains with synaptophysin, neuron specific enolase, chromogranin
 - » Treat with upfront chemotherapy: platinum + etoposide
- Sarcomatoid
 - » Treat with upfront cystectomy
- Carcinosarcoma
 - » Treat with upfront cystectomy

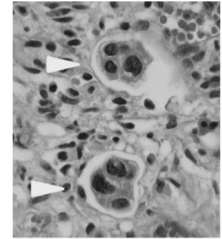


Variant Histology: From the Guidelines

- Pathologists need to report LVI and variant histologies
- 6. An experienced GU pathologist should review variant or suspected variant histologies (Moderate Recommendation; Evidence Strength: Grade C)
- 7. If a bladder sparing approach is considered, should perform a restaging TURBT within 4-6 weeks. (Expert Opinion)
- 8. Due to high rate of upstaging, clinician should consider offering initial radical cystectomy. (Expert Opinion)

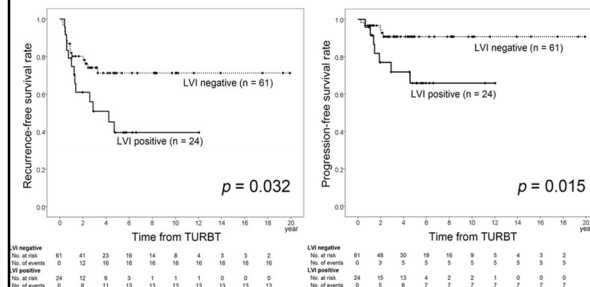
Impact of LVI on T1

- Small study of 116 T1 patients
- LVI in multivariate analysis
 - » In all patients, associated with stage progression (HR = 4.0)
 - » In patients treated with BCG, associated with:
 - Tumor recurrence (HR = 2.19)
 - Stage progression (HR = 3.76)



Fukumoto K, et al BMC Urol. 2016 Jan 19;16(1):5. doi: 10.1186/s12894-016-0122-1.

If LVI Negative—Higher RFS and PFS

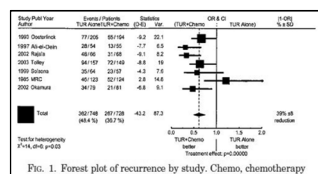


Fukumoto K, et al BMC Urol. 2016 Jan 19;16(1):5. doi: 10.1186/s12894-016-0122-1

NMIBC TREATMENT

Intravesical Therapies

15. Low- or intermediate-risk, consider single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT – **EXCEPT** with suspected perforation or extensive resection (Moderate Recommendation; Evidence Strength: Grade B)



Sylvester (2004)

FIG. 1. Forest plot of recurrence by study. Chemo, chemotherapy

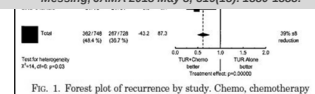
Intravesical Therapies

15. Low- or intermediate-risk, consider single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT – **EXCEPT** with suspected perforation or extensive resection

SWOG 0337 – Peri-operative single dose intravesical Gemcitabine 2g/100cc NS

- 35% recurrence rate with Gem (vs. 47% with NS)
 - Greater difference in low-risk subgroup (34% vs. 54%)
- Rare AEs: No grade 4 or 5 complications; no difference in Grade 3

Messing, JAMA 2018 May 8; 319(18): 1880-1888.



Sylvester (2004)

FIG. 1. Forest plot of recurrence by study. Chemo, chemotherapy

Intravesical Therapies

16. **Low-risk** - should not administer induction intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)
17. **Intermediate-risk** - consider administration of a 6 week induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)
18. **High-risk** patient with CIS, high-grade T1, or high-risk Ta, *should* administer 6-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)

Intravesical Chemo Mechanisms

- **Mitomycin**
 - » Bioreductive alkylating agent that crosslinks DNA
- **Anthracyclines** (doxorubicin, epirubicin, valrubicin)
 - » Topoisomerase inhibitor and DNA intercalator
- **Thiotepa**
 - » Alkalating agent
- **Gemcitabine**
 - » Pyrimidine analog and incorporated into DNA/RNA
- **Taxanes** (docetaxel, paclitaxel)
 - » Microtubule superstabilizing agent

Intravesical BCG

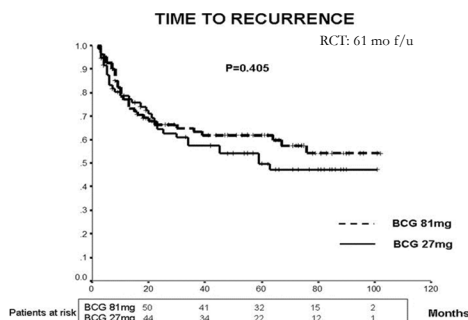
- Induction: weekly x 6 (5/6 considered adequate)
 - » Wait 2-6 weeks after TUR to start (or bleeding resolved)
- Maintenance: weekly x 3
 - » SWOG protocol 3, 6, 12, 18, 24, 30, 36 months
 - » 1 year full dose intermediate risk
 - » 3 year full dose high risk
- Dose
 - » May be reduced by 1/2 to 1/3 for tolerance
- Mechanism
 - » Th1 cellular immune response
 - » Increases IL-2, IL-12, IFN-gamma, TNF
 - » Decreases IL-10 and IL-4

Guidelines: BCG

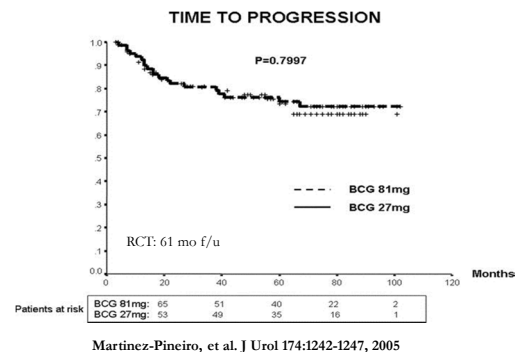
- **Insufficient evidence to recommend one strain of BCG**
 - Several small studies suggest that different strains may have different efficacies
- **Insufficient evidence to prescribe a particular BCG strength**
 - EORTC and CUETO studies
 - For lower-risk patients, no difference in recurrence free survival between full or 1/3 dose at 1 or 3 years of maintenance
- **There is insufficient evidence to recommend using BCG in combination with other intravesical agents (at this time...)**
 - Ongoing trials currently examining synergistic combinations

Rentsch 2014; Oddens 2013; Houghton 2013

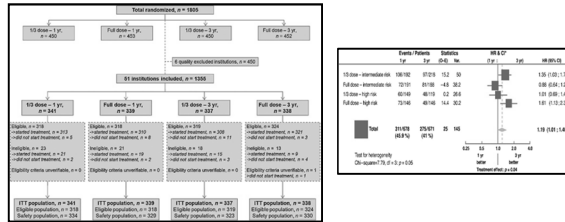
Reduced Dose BCG



Reduced Dose BCG

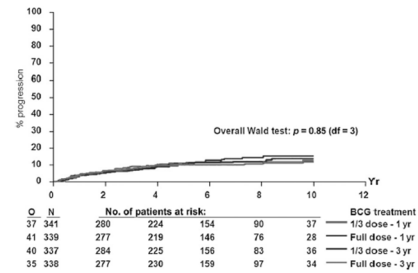


1 vs 3 years of Maintenance therapy (EORTC 30962)



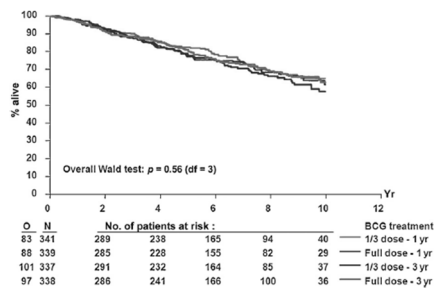
Oddens et al, EU (63), 2013

Time to Progression: No Difference



Oddens et al, Eur Urol, 2013

Survival Rates: No Difference



Oddens et al, Eur Urol, 2013

EORTC-GU Cancers Group: Conclusions

- No differences in **progression or survival rates** in any of the arms
- No difference in **morbidity** between 1/3 and full dose arms
- Subgroup analysis
 - Intermediate risk: no difference 1 vs. 3 years
 - High risk: 3 years associated with ↓ recurrence

Oddens et al, Eur Urol, 2013

Intravesical Maintenance Therapy

- Intermediate-risk** who completely responds to induction BCG, a clinician may utilize maintenance therapy. (Moderate Recommendation; Evidence Strength: Grade C)
- Intermediate-risk** who completely responds to induction BCG, should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)
- High-risk** who completely responds to induction BCG, should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)

Defining BCG Unresponsive Disease

- 6 month mark is important
- T1 disease
 - Persistent disease within 6 months after receiving at least 5/6 BCG doses
- CIS or Ta HG disease
 - Failed two prior BCG courses (5/6)
 - 5/6 induction; 2/3 maintenance
 - Progression to T1 at 3 months
- Consider upper tracts and prostatic urethra when patients are not responding (e.g. + Cytology only)

BCG Relapse

22. Intermediate- or high-risk with persistent or recurrent disease or positive cytology following intravesical therapy, should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)
23. In an intermediate- or high-risk with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, should offer a second course of BCG. (Moderate Recommendation; Strength of Evidence C)
 - » 50% patients with persistent/ recurrent NMIBC following first induction course of BCG respond to a second course of BCG

BCG Relapse

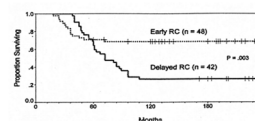
24. In patient fit for surgery with recurrent HG T1 after a single induction BCG, should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)
25. A clinician should not prescribe additional BCG if patient is intolerant or has recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within 6 months of 2 induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)
26. With persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses BCG, a clinician may recommend clinical trial enrollment. May offer intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)

Intravesical options in BCG-unresponsive disease

- Medically fit → Cystectomy
- What if medical unfit or refuse
 - » Clinical Trial
 - » Docetaxel (intravesical)
 - » Gemcitabine + Docetaxel (sequential)
 - » (Valrubicin)
 - » (Gemcitabine)

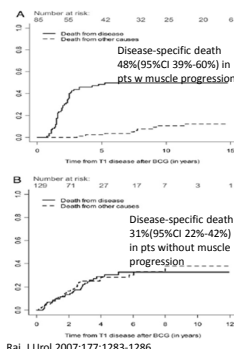
Role of Cystectomy

- Early, high-risk recurrences are at significant risk of progression; salvage intravesical therapies have poor success rates.
- Rationale for “early” cystectomy:
 - » Understaging (50% T1 are upstaged to ≥T2 at cystectomy)
 - » Significant “late” failure rate
 - » Potential survival benefit from avoiding delay of cystectomy



Waiting Until Progression May Prove Fatal

- A significant number of patients progress to detrusor muscle invasion
- Waiting for muscle invasion results in worse outcome supporting the role of early cystectomy in a select group of patients



Role of Cystectomy

27. Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)
28. High-risk who is fit for surgery with persistent HG T1 disease on re-TUR, or T1 tumors with CIS, LVI, or variant histologies, should consider initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)
29. In high-risk with persistent/recurrent disease within one year following treatment with two inductions of BCG or BCG maintenance, should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

NMIBC FOLLOW-UP

Risk-Adjusted Surveillance: Low Risk

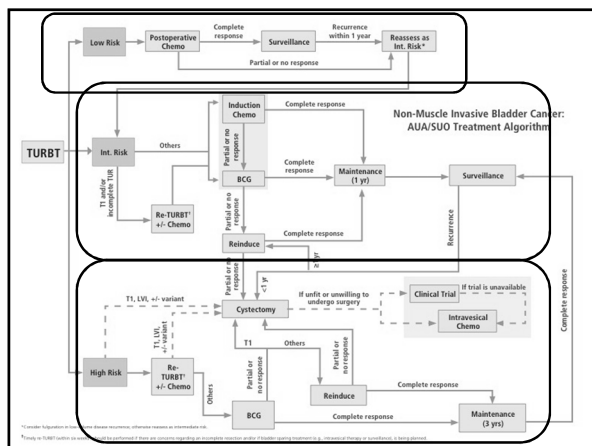
- First surveillance cystoscopy within 3-4 months
- Subsequent surveillance cystoscopy 6-9 months later
- Annually thereafter
- Surveillance after five years in absence of recurrence based on shared decision-making
- No need for routine cytology or upper tract imaging
- In-office fulguration an alternative to resection under anesthesia for small sub-centimeter papillary recurrences

Risk-Adjusted Surveillance: Intermediate Risk

- First surveillance cystoscopy within 3-4 months
- Subsequent surveillance cystoscopy every 3-6 months for 2 years
- Then 6-12 months for years 3 and 4
- Annually thereafter
- Upper tract surveillance imaging every 1-2 years

Risk-Adjusted Surveillance: High Risk

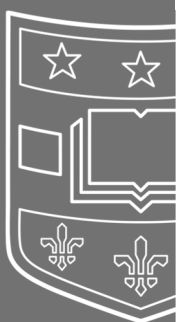
- First surveillance cystoscopy within 3-4 months
- Subsequent surveillance cystoscopy every 3-4 months for 2 years
- Then every 6 months for years 3 and 4
- Annually thereafter
- Upper tract surveillance imaging every 1-2 years



Intravesical Therapy for Management of Non-Muscle-Invasive Bladder Cancer

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Disclosure statement

- Nothing to disclose



Bladder cancer basics

- Estimated 81,000 new cases of bladder cancer and 17,000 bladder cancer deaths predicted in the U.S. in 2018.¹
- Approximately 75% of newly diagnosed bladder cancer is non-muscle-invasive bladder cancer (NMIBC).²
- Recurrence occurs in 50-70%, progression occurs in 10-40%.^{2,3}
- NMIBC is a heterogeneous group
 - Important to identify and risk stratify those with higher risk of recurrence/progression.

1. Siegel et al. (2015) *CA: A Canc J for Clin.*
2. Sylvester et al. (2006) *Eur Urol.*
3. Fernandez-Gomez et al. (2009) *J Urol.*



NMIBC: staging and detection

Washington University in St. Louis



AUA/SUO Guidelines on NMIBC (2016)

- Low-risk:
 - Solitary LGTa tumors ≤3cm and PUNLMP.
- Intermediate-risk:
 - LGTa recurrences within 1 year, solitary LGTa >3cm, multifocal LGTa, HGTA tumors ≤3cm, LGT1.
- High-risk:
 - HGT1, recurrent HGTA, HGTA >3cm, multifocal HGTA, CIS, BCG failure in HG patient, variant histology, +LVI, any HG prostatic urethra involvement.

Chang et al. (2016) *J Urol.*



“Highest-risk” NMIBC

- Patients with HGT1 and *concomitant* CIS are at the highest risk, with progression rates around 50% and a 34% risk of death from bladder cancer.¹
 - EORTC data suggests patients with HGT1 and CIS have rates of progression of 29% and 74% at 1 and 5 years, respectively (compared to 10% and 29% in HGT1 alone).²
 - Meta-analysis of 15,215 patients showed that HGT1 with CIS carried a two-fold risk of progression when compared to HGT1 alone.³

1. Cookson et al. (1997) *J Urol.*
2. Dhir R. (2007) *Yearbook of Path and Lab Med.*
3. Martin-Doyle et al. (2015) *J Clin Oncol.*



Role of repeat TURBT

- Up to 77% have residual tumor and 15-29% upstaged.^{1,2}
 - Up to 50% upstaged in HG1 patients when muscle not in original specimen.
 - Change in management in 1/3 patients.
- Re-TURBT reduces the frequency of early tumor recurrences and is thought to improve PFS.^{1,2}
- Pathology on re-TURBT can be utilized as a prognostic indicator.
 - Residual HG1 at re-TURBT associated with increased risk of recurrence and progression.²
 - 2-year RFS only 26%.³
 - 23-82% risk of progression to MIBC (vs 6-19% without HG1 on re-TURBT).^{3,4}

1. Herr HW. (1999) J Urol. 3. Tao et al. (2017) PLoS ONE.
2. Gandy et al. (2016) BJU Int. 4. Herr et al. (2007) J Urol.

Blue-light cystoscopy

- Recurrence rates of NMIBC (all path) after white light cystoscopy (WLC) re-TURBT are 41%, 61%, and 73% at 2, 12, and 36 months.¹
 - WLC detection of CIS can be as poor as 61%.¹
- Due to the high rates of recurrence and upstaging seen on WLC re-TURBT, new techniques have emerged → blue light cystoscopy (BLC).
- Meta-analysis of RCTs: BLC with 5-aminolevulinic acid (5-ALA) or hexaminolevulinate (HAL) improves detection rate of CIS to ~90%.²
 - HAL (Cysview®) was approved by the FDA in 2010.
 - Meta-analysis of BLC with HAL associated with improved detection rates of Ta, T1, and CIS (decreased recurrence at 12 months; 35% vs 45%).³
- NB: while BLC associated with improved RFS at 1 and 2 years, progression to MIBC not improved.⁴

1. Danilchenko et al. (2005) J Urol. 3. Burger et al. (2013) Eur Urol.
2. Grossman et al. (2007) J Urol. 4. Yuan et al. (2013) PLoS ONE.

Intravesical treatments: Overview

Washington University in St. Louis

Intravesical treatments: the basics

- Delivery of medication directly to the site of the tumor
 - Minimizes systemic exposure
- Held in the bladder for as long as tolerable (ideally 2 hrs)
- Increased concentration by decreasing urine production
- Done in absence of bladder perforation and/or UTI
- Concepts:
 - Perioperative vs induction vs maintenance
 - Chemotherapy vs immunotherapy
 - Treatment vs prophylaxis

Intravesical treatments: the basics

- Who is a candidate?
 - AUA/SUO low-risk
 - Perioperative
 - AUA/SUO intermediate-risk
 - Induction +/- maintenance
 - AUA/SUO high-risk
 - Induction +/- maintenance
 - MIBC?
 - NMIBC recurrence after bladder preservation therapy
 - Clinical trials
 - NAC delivery

Intravesical treatments: the agents

- Chemotherapy
 - Mitomycin C, doxorubicin, epirubicin, valrubicin, gemcitabine, thiotepa, docetaxel, paclitaxel
 - Combination: gemcitabine/docetaxel
- Immunotherapy
 - BCG, interferon- α , γ PD-1/PD-L1
 - Combination: BCG/interferon

Intravesical treatments: the agents

Agent	Mechanism of Action
Immunomodulatory Agents	
Bacillus Calmette-Guérin (BCG)	- Inflammatory host response; release of cytokines - May be combined with interferons^{99,104}
Interferons	- Lymphocyte activation; cytokine release; phagocyte stimulation - Antiproliferative actions - Antiangiogenic^{11,90}
Chemotherapeutic Agents	
Thiotepa	Alkylating agent; cross-links nucleic acids⁹⁵
Mitomycin C	Antibiotic; inhibits DNA synthesis^{36,78}
Doxorubicin, epirubicin, valrubicin	Intercalating agents; inhibits DNA synthesis^{75,98,98}
Gemcitabine	Deoxycytidine analog; inhibits DNA synthesis^{99,103}

Figure from AUA Guidelines. (2007)

Intravesical treatments: the take-homes

- BCG, mitomycin, doxorubicin, and epirubicin are associated with a reduction in recurrence risk by 20-44%.
- BCG is associated with a decreased risk of progression by 5%.
 - Although interferon- α has been associated with a decreased risk of progression, finding was based on 2 flawed RCTs.
- No intravesical agent (including BCG) is associated with a decreased risk of all-cause or bladder cancer-specific mortality.
 - Likely secondary to limitations of study design.

Chou R et al. (2017) J Urol.

Intravesical immunotherapy: BCG

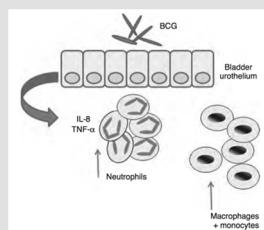
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Immune system and the bladder: a primer

- PAMPs $\rightarrow$ TLR2 on tissue-resident macrophage $\rightarrow$ cytokines and chemokines
 - Urothelial cells $\rightarrow$ secrete type I IFN (alpha and beta)
 - Macrophages $\rightarrow$ engulfs pathogens $\rightarrow$ cytokines and chemokines
- Th1 response vs Th2 response

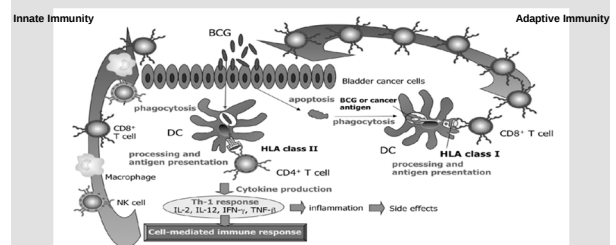
BCG mechanism of action

Do we really know?



Courtesy of Steinberg GD.

BCG Immunology Targets



Kitamura et al. (2011) Cancers
Shelley et al. (2006) Cochrane Data of System Rev.

History of BCG

- 1929 – Autopsy study: lower frequency of cancer in patients with active/healed TB
- 1950s (Old et al) – Mice infected with BCG show resistance to tumor transplant
- 1970s (Zbar et al) – delayed hypersensitivity rxn to BCG caused tumor inhibition
- 1975 (deKernion et al) – treated melanoma of bladder with intravesical BCG
- 1976 (Morales et al) – first successful use of intravesical BCG for non-invasive UC
 - Devised original protocol for induction:
 - 6 doses: Frappier strain packaged in 6 vials
 - 120 mg/dose: tolerated via intradermal route
 - Weekly instillation: adverse effects <1 week
- 1978 (Morales et al) – 7/10 patients exhibit tumor response in bladder
- Two RCTs, SWOG (Lamm) and MSKCC, confirmed reduced tumor recurrences compared to TURBT alone
- 1990 – FDA approved intravesical BCG

Herr et al. (2008) J Urol.
Agarwal PK. NIH/NCI
data

BCG

- BCG is the gold standard adjuvant treatment for patients with HR NMIBC.
- BCG is used as the predominant (>2:1 majority) intravesical agent in North America, even in low/intermediate risk bladder cancer.
- Numerous studies demonstrate reduction in both recurrence and progression.¹⁻³
- Numerous studies have supported the efficacy of intravesical BCG as a treatment for CIS.
 - Lamm et al reviewed 34 series (1,354 patients) and noted an average CR rate of 72% in CIS patients.⁴
 - Response is durable in ~30% at 10 years

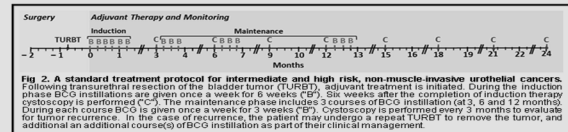
1. Morales et al. (2017) J Urol. 3. Lamm et al. (2000) J Urol.
2. Babjuk et al. (2017) Eur Urol. 4. Lamm et al. (1995) Oncol.

BCG maintenance

- SWOG 8507¹ compared induction vs induction + 3 years of maintenance.
 - 3 weekly instillations at 3, 6, 12, 18, 24, and 36 months.
 - Overall CR rate increased from 56% to 82% with additional maintenance treatments.
 - However, the vast majority did not complete the 3-year schedule due to toxicity.
- EORTC-GU Cancers Group Randomized Study² compared 1/3D vs FD and 1 yr vs 3 yr
 - Intermediate-risk: FD-1 yr equal to FD-3 yr
 - High-risk: FD-3 yr has lower recurrence rate (similar progression/death)
- The AUA recommends induction BCG followed by 1-3 years of maintenance, depending on risk.³

1. Lamm et al. (2000) J Urol.
2. Oddens et al. (2013) Eur Urol.
3. Chang et al. (2016) J Urol.

BCG treatment protocol



BCG failure

- Despite aggressive treatment with BCG...
 - ~20-65% (avg ~40%) recur
 - ~20-40% progress
 - And many some won't tolerate treatment.
- ~15,000 patients per year are deemed a BCG "failure" to some degree

BCG failure

- Those that recur after BCG require second line therapy, most of which—outside of radical cystectomy—are not effective.
- However, there is wide heterogeneity among BCG failures:
 - Papillary vs CIS, LG vs HG, number of failed courses, time of failure, failure during maintenance
 - Even the terms BCG refractory/resistant/failure have different meanings to different people

BCG Failure Definitions

BCG-relapsing	Recurrence after achieving 6 months of DFS
BCG-intolerant	Less than adequate course of therapy terminated due to serious adverse event
BCG-refractory	Failure to achieve DFS at 6 months after initial BCG therapy if on maintenance Or Failure to achieve DFS at 3 months after initial BCG therapy if retreated
BCG-resistant	Disease improves then resolves after 6 months of treatment but is evident at 3 months

Lerner et al. (2015) *Bladder Cancer*.

BCG-unresponsive: HR NMIBC unlikely to benefit from further intravesical BCG

- Patients that don't respond to intravesical BCG and have a new or persistent HG recurrence at 6 months after initiation of BCG
- Have received at least two courses of BCG
 - The "5+2" rule: at least 5/6 + at least 2/3
- Relapse within six months of last instillation with HG NMIBC
- All papillary NMIBC should be completely resected prior to BCG

Lerner et al. (2015) *Bladder Cancer*.

BCG: leftovers

- AUA/SUO guidelines:¹
 - May offer a second induction course
 - Up to 30% of patients with CIS will achieve additional response
- EORTC 30911:²
 - Elderly patients (>70 yo) may respond poorer, but BCG still provides favorable response over chemotherapy

1. Chang et al. (2016) *J Urol*.
2. Oddens et al. (2014) *Eur Urol*.

Intravesical chemotherapy: Overview

Washington University in St. Louis

Intravesical chemotherapy

- Historically, when compared to BCG, intravesical chemotherapy has not been highly efficacious
- Much of this is secondary to the high efficacy of BCG
 - Chemotherapy must be better than BCG to be front-line (which it is not)
 - Therefore, it is often second-line treatment
 - Second-line treatment by nature will have worse outcomes

Intravesical chemotherapy: when and why?

- Perioperative treatment
 - Mitomycin C
 - Gemcitabine
- Induction +/- maintenance
 - Primary
 - Mitomycin C
 - BCG-unresponsive
 - Mitomycin C
 - Valrubicin
 - Gemcitabine/docetaxel

Intravesical chemotherapy: Perioperative

Washington University in St. Louis

Mitomycin C

- Primary use is in perioperative chemotherapy
 - 39% reduction in recurrence (OR 0.61 single tumor, OR 0.44 multiple tumors)¹
 - Average CR for initial treatment ~35% if single tumor
- Can be used for induction therapy, but maintenance has no strong evidence
- Non-cell cycle specific; LG cells tend to be sensitive
 - May be used for induction therapy of intermediate-risk patients with LG tumors
- Side effects
 - Leukopenia - rare
 - Chemical cystitis – up to 40% of patients
 - Contraction/decreased capacity
 - Calcification
 - Pain

1. Sylvester et al. (2004) J Urol.

Gemcitabine

- Can be used in perioperative setting
- More readily available, less costly, less toxic than mitomycin C
- SWOG S0037:
 - 4-yr recurrence 35% vs 47% with saline (HR 0.66, p<0.001)
 - For low-risk, 34% vs 54% (HR 0.53, p<0.001)
 - Direct comparison to mitomycin C not performed due to large sample size requirement
- New standard of care for perioperative chemo?

Messing et al. (2018) JAMA.

Poor utilization

- Despite supportive evidence, use remains low in U.S. (1-16%)¹
 - Access?
 - Cost?
 - Unknown histology?
 - Unnecessary treatment for some
 - Real benefit?
 - Randomized study comparing postoperative saline CBI to mitomycin²
 - No difference in progression, time to recurrence, or 5-year RFS
- May improve with adoption of gemcitabine

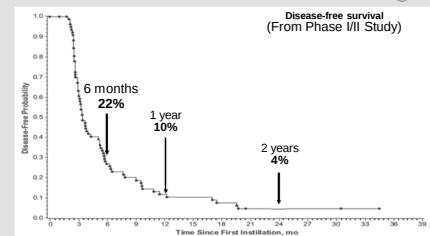
1. Cookson et al. (2012) J Urol.
2. Onishi et al. (2017) BJU Int.

Intravesical chemotherapy: BCG unresponsive

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Valrubicin

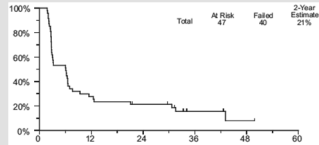
- For CIS that are either BCG unresponsive or non-candidate
- Gained FDA approval for CIS post BCG



Dinney et al. (2013) Urol Oncol.

Gemcitabine

- SWOG S0353: PhII Trial of gemcitabine with recurrence after two induction courses of BCG
 - 47 patients (89% HG, 11% multifocal LG)
 - Induction + once monthly x 1 yr
- 3 month CR: 47%
- 2 year CR: 21%



Skinner et al. (2013) J Urol.

Gemcitabine/docetaxel

- 33 patients, full induction course
- Median DFS: 6.5 mos (42% 1-yr and 24% 2-yr DFS).
- Median HG-RFS: 17.1 mos (56% 1-yr and 42% 2-yr HG-RFS).
- Median HG-RFS (among pts with HG path): 15.7 mos (51% 1-yr HG-RFS and 34% 2-yr HG-RFS).
- No significant predictors for HG-RFS or DFS.
- 5 LG recurrences, and 16 HG recurrences, with 6 progressions among these. 7 (21%) underwent RC at a median of 14.9 mos.

Milnar et al. (2017) Presented ASCO.

Intravesical immunotherapy: BCG unresponsive

Washington University in St. Louis

Intravesical immunotherapies

- Mycobacterial Cell Wall Nucleic Acid Complex (MCNA)
- Interferon- α 2b (IFN)
- Recombinant adenovirus-mediated IFN- α 2b (Instiladrin)

Mycobacterial Cell Wall Nucleic Acid Complex

- Phase III trial: 129 patients with prior BCG failure
 - CIS only (59 patients)
 - Ta-T2 tumors only (38 patients)
 - CIS and Ta-T2 tumors (32 patients)
- Intravesical MCNA given with induction + 3 week maintenance at 3, 6, 12, 18, and 24 months
- 3 year follow-up, median follow-up 34 months
- 1-yr DFS: 21%

Morales et al. (2015) J Urol.

Interferon alpha-2b

- Pleiotropic immune modulator with anti-proliferative activity. Well tolerated as an intravesical single agent
- Multicenter RCTs in 1996 and 1997 found Interferon alone was less effective than MMC or BCG
 - Dose-dependent response; 12-20%
- BCG+IFN trial in 2001 for BCG failures
 - 1-2 year success rates of 40-45%, improved with 2nd course and maintenance
- No difference BCG vs BCG/IFN in BCG-naïve patients

Boccardo F, et al. JCO 1994
Jimenez-Chaz JE et al. Urology 1997
O'Donnell MA et al. J Urol 2001
Joudi FN et al. J Urol 2006

Instiladrin (rAd-IFN/Syn3)

- Syn3 is a novel medium that facilitates intravesical adenovirus vector mediated transduction of IFN-α
- Open Label Phase I trial assessed 17 patients
 - Detectable urine IFN-α >10 days following transduction
 - Minimally detectable serum IFN-α (peaked in 24 hours)
 - No Grade 3+ adverse events
 - 40% patients with complete response

J Urol. 2013 September ; 190(3): 850–856.

Instiladrin (rAd-IFN/Syn3)

- Phase II open label study - Completed
 - BCG-unresponsive NMIBC population (n=40)
 - 35% 1 year RFS (50% RFS in papillary; 29% RFS in CIS)
- Phase III open label study - Ongoing
 - Plan to enroll 135 patients
 - Single intravesical instillation, further maintenance doses given after 3, 6, 9 month surveillance cystoscopies
 - Primary outcome: 12 month complete response

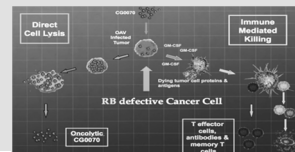
Novel intravesical immunotherapies

- Vaccinia Virus
- Vicinium (VB4-845)
- CG0070 Oncolytic Adenovirus
- Gp96 (Heat Biologics ImPACT)
- ALT-803 (IL-15 superagonist)
- Imiquimod (TMX-101)

A First in Human Phase 1 Study of CG0070, a GM-CSF Expressing Oncolytic Adenovirus, for the Treatment of Nonmuscle Invasive Bladder Cancer

James M. Burke,^{*,†} Donald L. Lamm,[‡] Maxwell V. Meng,[§] John J. Nemunaitis,[¶] Joseph J. Stephenson, James C. Arseneau,[‡] Junko Aimi, Seth Lerner, Alex W. Yeung,[§] Troy Kazarian,^{||} Daniel J. Maslyar[§] and James M. McKiernan

- CG0070 – Oncolytic Adenovirus targeting RB defective pathway mutations
- Phase I trial assessed 35 patients
- Open Label, dose escalation



THE JOURNAL OF UROLOGY®
Vol. 188, 2391-2397, December 2012

A First in Human Phase 1 Study of CG0070, a GM-CSF Expressing Oncolytic Adenovirus, for the Treatment of Nonmuscle Invasive Bladder Cancer

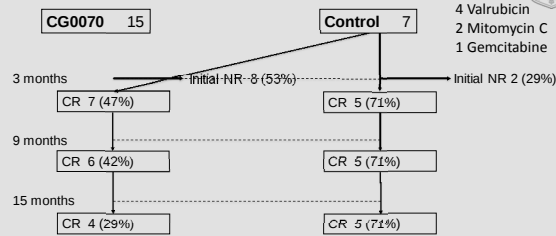
James M. Burke,^{*,†} Donald L. Lamm,[‡] Maxwell V. Meng,[§] John J. Nemunaitis,[¶] Joseph J. Stephenson, James C. Arseneau,[‡] Junko Aimi, Seth Lerner, Alex W. Yeung,[§] Troy Kazarian,^{||} Daniel J. Maslyar[§] and James M. McKiernan

Subgroups Examined	N	Complete Response "CR" Rate @ 3 months (CR/n)	Median Duration of Complete Response (months)
All Patients	35	48.6% (17/35)	10.4
Multiple Dose Subgroups combined (4 weekly + weekly X 6)	22	63.6% (14/22)	16.1
4 Weekly	13	53.9% (7/13)	15.3
Weekly X 6	9	77.8% (7/9)	36
pRb(~and high) in Multiple Dose Subgroups Combined	11	81.8% (9/11)	25
pRb (~and high) in Weekly X 6	5	100% (5/5)	Not Reached

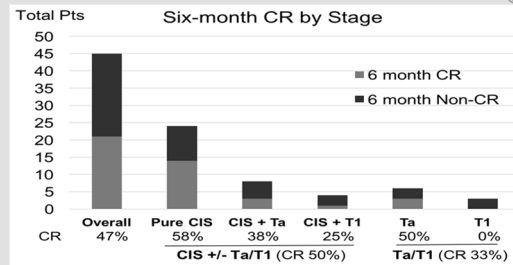
CG0070 Phase III Trials

- Bond I – Study Design
 - CIS and CIS with Ta and/or T1 disease
 - Randomized 2:1 with CG0070: control regimens
 - 6 week induction course
 - 3 and 9 month assessments
 - 15 month response as complete response
- Bond II
 - Open label HR NMIBC with Maintenance

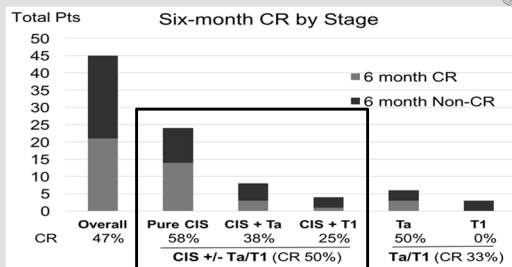
Bond I Response Rates



BOND II Response Rates



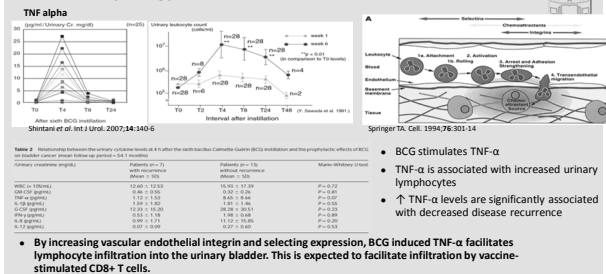
BOND II Response Rates



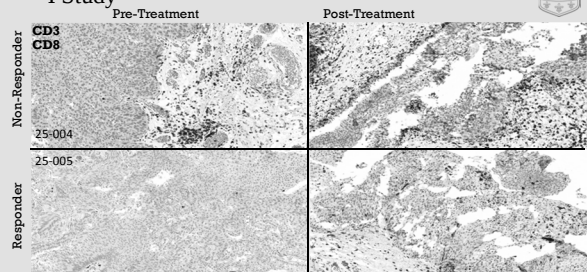
Heat Biologics Intradermal Vaccine HS-410

- HS-410: an engineered "bladder tumor" cell line with added gp96 heat shock protein
- Produces bladder tumor antigens
- Produces an extracellular gp96 to continually deliver tumor antigens to CD8+ cells
- Administered intradermal, aim to be in combination with BCG
- Goal is for superior CD8+ activation relative to BCG alone

Potential Synergy Between BCG & HS-410



Evidence of CD8+ Tumor Infiltration in HS-410 Phase I Study



• HS-410: Phase I Preliminary Clinical Outcomes

Pt	1	2	3	4	5	6	7*	8	9	10	11	12	13	14	17	21*	29	53
23-1	T2/CIS																NED	
23-2	T1																T1 no CIS → T1 + CIS (40)	
25-1	Ta*						Tb											
25-2	T1/CIS																NED	
25-3	T1																NED	
25-4	T1/CIS																T1 → CIS → Ta w/o CIS at Wk 7 → T1 → CIS at Wk 13	
25-5	T1						Ta										NED	
12-1	T1																NED	
25-7	T1*																NED	
25-8	Tb																NED	

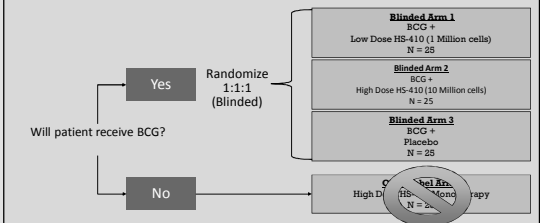
*Cystoscopy to assess disease recurrence
*Recurrent disease >12 mo since last BCG

as of 14-Apr-2015

3 of 4 pts with CIS are disease-free

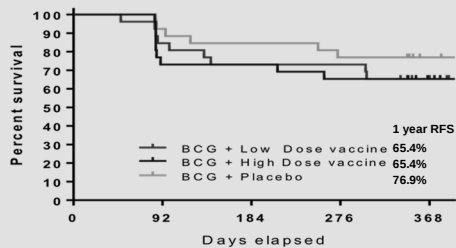
HS-410: Phase II Trial

Phase II, Randomized, Blinded, Placebo-controlled trial
Primary Endpoint: 1-year recurrence free survival



HS-410: Phase II Trial

Recurrence Free Survival, ITT pop.



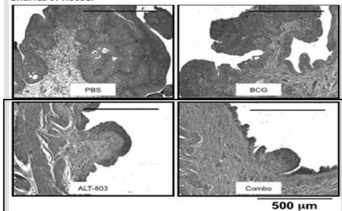
Intravesical ALT-803 and BCG Treatment Reduces Tumor Burden in a Carcinogen Induced Bladder Cancer Rat Model; a Role for Cytokine Production and NK Cell Expansion

Evan Gomes-Giacola^{1,2}, Makito Miyake^{1,2}, Steve Goodison^{1,2}, Aravindhan Sriharan³, Ge Zhang¹, Lijiang You⁴, Jack O. Egan⁵, Peter R. Rhode⁶, Alexander S. Parker⁷, Karl X. Chai⁸, Hing C. Wong⁹, Charles J. Rosser^{1,2,4}

- IL-15 stimulates T-cell and natural killer cell responses through IL-12 pathway
- But with less capillary leak/adverse events
- ALT-803: Complex of IL-15 super-agonist and dimeric IL-15 fusion protein
- Enhanced *in vivo* activity relative to IL-15 in mice
- Preliminary study performed in rats w/ NMIBC

Intravesical ALT-803 and BCG Treatment Reduces Tumor Burden in a Carcinogen Induced Bladder Cancer Rat Model; a Role for Cytokine Production and NK Cell Expansion

Evan Gomes-Giacola^{1,2}, Makito Miyake^{1,2}, Steve Goodison^{1,2}, Aravindhan Sriharan³, Ge Zhang¹, Lijiang You⁴, Jack O. Egan⁵, Peter R. Rhode⁶, Alexander S. Parker⁷, Karl X. Chai⁸, Hing C. Wong⁹, Charles J. Rosser^{1,2,4}



- Greatest bladder wall thickness decrease w/ALT-803 or ALT-803+BCG
- Greater increase in cytokines: IL-1a, IL-1b, RANTES
- 76% reduction in angiogenesis
- Currently phase 1 trial for multiple myeloma

PD-L1 as a resistance mechanism to BCG

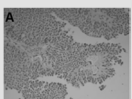


Figure A: PD-L1(-) NMIBC

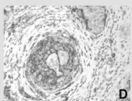
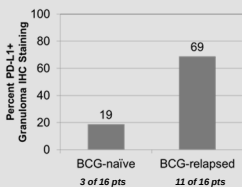


Figure B: PD-L1(+) NMIBC Post-BCG Treatment Granuloma

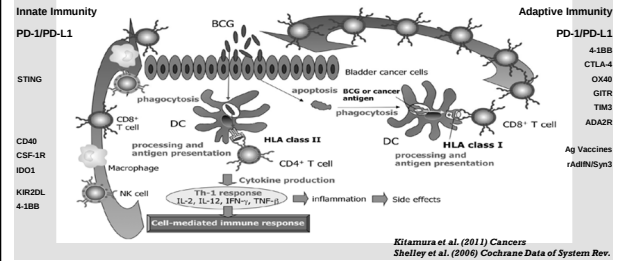


Imman et al. (2007) Cancer.

Future directions

Washington University in St. Louis

BCG Immunology Targets



Neoantigen vaccines

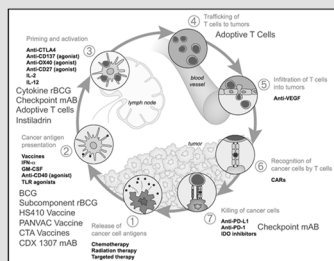
- Personalized neoantigen vaccines (NAV) induce broad immune responses, suggesting potential for synergy with an immune checkpoint inhibitor.¹
- Two clinical trials are currently underway evaluating combination therapy with NAV + immune checkpoint inhibitor in UC.
 - NEO-PV-01 + nivolumab (NCT02897765)
 - PGV001 + atezolizumab (NCT03359239)
- Currently aimed at metastatic disease, but goal is to harness immune system to treat cancer in primary as well.

1. Ott et al. (2017) Nature.

Immune checkpoints

- Normally immune checkpoints allow for self-tolerance
- Tumor cells exploit this regulatory pathway by over-expression of immune checkpoint molecules
- Therefore, novel therapies utilize monoclonal antibodies to block either the:
 - Immune checkpoint receptor (CTLA-4 or PD-1)
 - Immune checkpoint ligand (B7 or PD-L1)

Therapeutic targets



Chen ED. (2013) Immunity.

Timing of checkpoint inhibition

- Given highly successful utilization in metastatic setting, can timing be altered?
 - BCG unresponsive disease?
 - Neoadjuvant for MIBC?
 - Adjuvant for high-risk MIBC?

Current phase II trials



- KEYNOTE-057
 - Pembrolizumab x 2 year (n=260)
- S1605
 - atezolizumab x 1 year (n=148)
- WO29635 (GU 123)
 - atezolizumab monotherapy (BCG-refractory NMIBC)
 - atezolizumab + BCG
 - 1/3 vs 2/3 vs full dose BCG
 - BCG refractory vs BCG relapsing vs BCG-naïve NMIBC
- ADAPT-BLADDER (HCRN 16-243)
 - Durvalumab + BCG
 - Durvalumab + EBRT
 - BCG alone → Durvalumab if residual NMIBC

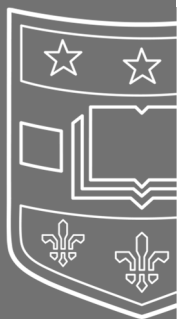
Ongoing issues/barriers



- Inherent limitations of single-arm trial design
- Shortcomings in mechanism of action (MoA)
- Reliability of DFS assessments
- Failure of reaching efficacy endpoints
- Inherent heterogeneity of CIS vs Ta/T1 patients
- Possible approval due to lack of treatments (BCG shortage)
- Current regulatory landscape in NMIBC

Thank you.

 Washington University in St. Louis



 Memorial Sloan Kettering Cancer Center.

Surgical Management of Invasive Bladder Cancer:

Bernard H. Bochner, MD
Attending Surgeon, Urology Service
Sir Murray Brennan Chair in Surgery
Memorial Sloan Kettering Cancer Center

Presenter Disclosures

Genentech: Chairman of Independent Data Safety monitoring committee

Olympus: Faculty, endoscopy training course

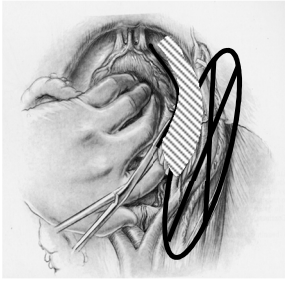
 Memorial Sloan Kettering Cancer Center.

Radical Cystectomy For Bladder Cancer: GOALS

- Local-regional control is the primary goal
- Surgical technique is critical
 - Key components: wide excision and PLND
- Surgical quality matters
 - Poor surgery leads to poor outcomes

 Memorial Sloan Kettering Cancer Center.

Simple Cystectomy: Lateral Dissection



- First performed 1888 (Bardenheuer)
- Simple cystectomy
 - Adherent/adjacent fat only
 - No regional lymph node dissection
- Stage procedure
 - ureteroenterostomy
 - cystectomy

 Memorial Sloan Kettering Cancer Center.

Cystectomy and Ureteroenterostomy: Operative Mortality and Survival

Author	Year	# patients	Mortality	Tumor recurrences
Hinman	1939	25	40%	53%
Priestley and Strom	1943	71	35%	31%
Jewett	1944	39	33%	50%
Smith	1947	47	21%	40%
Marshall	1947	81	16%	23%
Edelman	1947	34	29%	50%
Ferris and Priestley	1948	119	13%	37%

 Memorial Sloan Kettering Cancer Center.

Adapted from: Leadbetter and Cooper, J. Urol., 1950

Radical Cystectomy For Bladder Cancer: Lessons From Past

- 100 consecutive cystectomy patients
 - Little emphasis toward perivesical tissues and no regional LN dissection
- 26% "successful" 2 year outcomes
- 38 patients with persistent pelvic disease

"The implications seems unavoidable that a more radical procedure might be worthy of trial..."

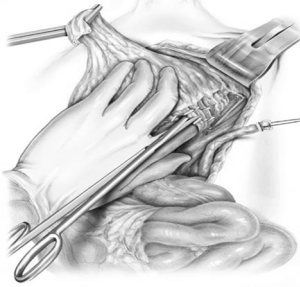



 Memorial Sloan Kettering Cancer Center.

Marshall and Whitmore, J. Urol., 1950

Bladder Cancer: What we know

- Established surgical principles for Radical Cystectomy



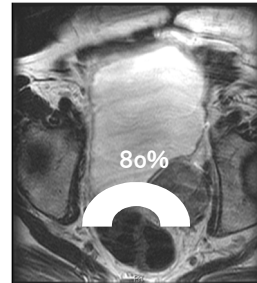
Wide excision of the bladder and perivesical tissues



Bochner, Skinner et al in *Comprehensive Textbook of Genitourinary Oncology*. 2011.

Radical Cystectomy and PLND

Local Recurrence



Memorial Sloan-Kettering Cancer Center

Radical Cystectomy and PLND

Local Recurrence

- Associated with stage of primary tumor
 - 6% OC; 13% NOC; (9% overall) (Stein et al JCO, 2001)
- Associated with **soft tissue surgical margin status**
 - 6% vs 21% (Dotan et al, J Urol 2007)
- Symptoms: pain (pelvic, perineal, lower extremity); bleeding; lower extremity or penile edema; bowel obstruction; constipation or priapism
- median time to a local recurrence 8-18 months
- median survival ranges from 4-8 months



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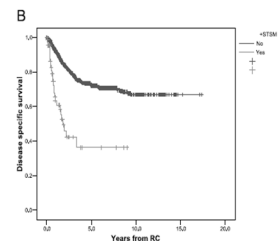
Soft Tissue Margin Status

MSKCC Radical Cystectomy Experience (1985-2005)

Effects on Disease Specific Survival

Variables Associated with Disease Specific Death on Multivariate Analysis

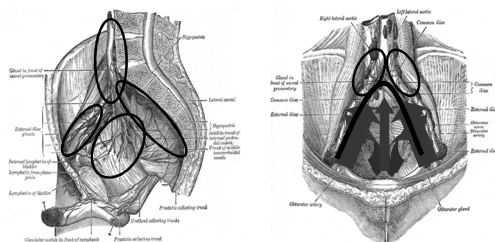
VARIABLE	HR	P VALUE
Pathologic stage	1.96	0.001
Vascular invasion	1.72	0.001
Positive STSM	1.98	0.008
Lymph node	1.88	0.001
No. LN removed	0.97	0.001



Memorial Sloan-Kettering Cancer Center

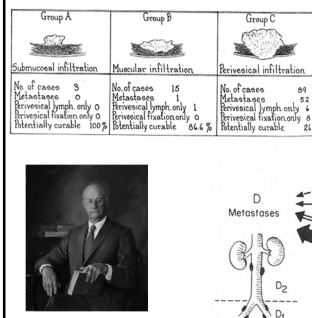
Dotan et al, J Urol 2007

Bladder: Lymphatic Drainage



Cuneo and Marcille: Bull. Mem. De la Soc. Anat. de Paris, 3:649, 1901

Bladder Cancer: What we know



Memorial Sloan-Kettering Cancer Center

Jewett and Strong, J. Urol., 1946

Regional Lymph Node Involvement By Bladder Cancer

Author	Year	# patients	Pathologic Stage (% Node +)			
			P1	P2	P3	P4
Ghoneim et al	1997	1,026	6	16	42	36
Leissner et al	2000	447	10	20	49	75
Stein et al	2001	1,054	7	22	44	42



Role of Lymphadenectomy At Radical Cystectomy For Bladder Cancer?

Therapeutic Benefit



MSKCC Early Experience With Node Positive Bladder Cancer

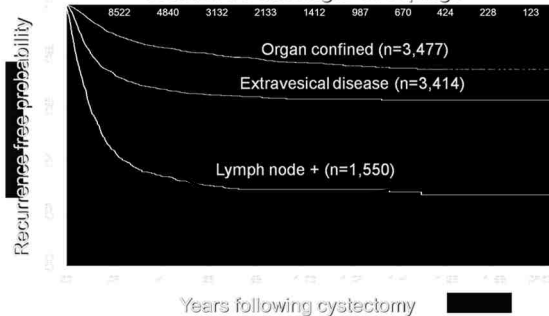
Survival From Radical Surgery of 100 Patient with Bladder Carcinoma, According to Stage and Grade

Survival years	Grade III or IV, & Stage O, A, or B1 (9 pts)		Grade III or IV, & Stage B2, C, D (65 pts)		Stage D, regardless of grade (32 pts)	
	No.	%	No.	%	No.	%
1	7	77	25	38	7	22
2	6	67	14	22	3	9
3	5	56	8	12	1	3
4	5	56	7	11	1	3



Whitmore and Marshall, Cancer, 1956

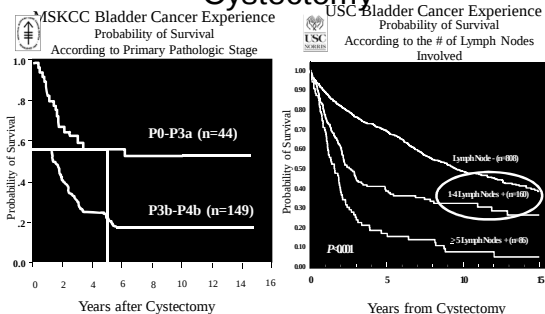
International Bladder Cancer Consortium: Probability of Not Recurring Standard Pathologic Groupings



J Clin Oncol 2006; 24(21):3951-72

© 2014 MSKCC

Expected Outcome of Node Positive Disease Following Cystectomy

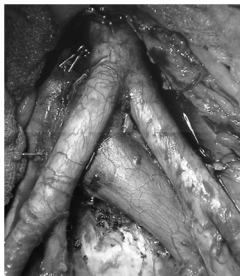


Role of Lymphadenectomy in Bladder Cancer

Extent of Dissection?



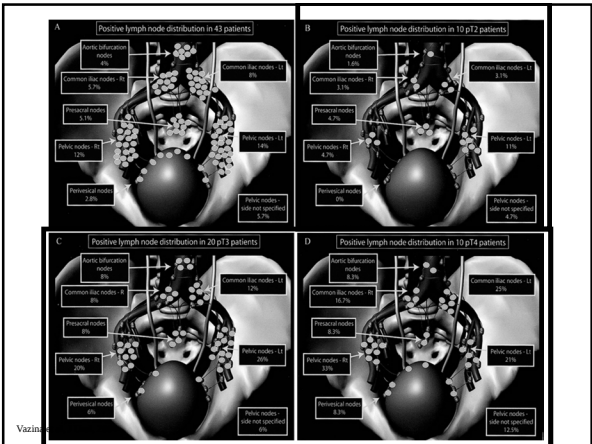
Bladder Cancer: PLND



- 130 cystectomy, NO gross LN+
- 88% with common iliac limits
- Mean 34±14 nodes removed
- 18 pts. (14%) microscopically +LN
 >17 pts. with 1 or 2 +LN



Wishnow, J. Urol., 1987



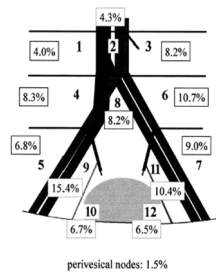
Surgical Management: European Cooperative Study

- 290 TCC and SCC patients rad cystectomy and extended LN at 6 centers
- 73% of 290 had tissue removed from all regions
- 28% of patients with + LN
- If only obturator nodes removed: 74% (444/599 +LN) left behind
- 6.9% with nodes only above bifurcation of common iliac vessels

RECOMMENDED EXTENDED DISSECTION ON ALL UNDERGOING RADICAL CYSTECTOMY



Leissner et al, J Urol, 2004



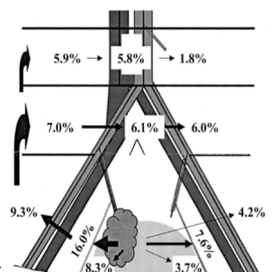
Surgical Management: European Cooperative Study

- 119 patients with strictly unilateral primary tumors
- 32 patients with + LN
- 23% with nodes involved the CONTRALATERAL SIDE
- (Jensen et al 24% with contralateral LNs)

ALL LYMPH NODE DISSECTIONS BE PERFORMED BILATERALLY



Leissner et al, J Urol, 2004



Surgical Quality For Invasive Bladder Cancer

Is There A Recognized Standard For The Number Of Nodes That Should Be Resected?



Extent of Lymphadenectomy MSKCC Prospective LN Study

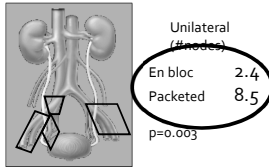
	Surgeon 1 (n=59 pts)	Surgeon 2 (n=39 pts)	Surgeon 3 (n=33 pts)	Surgeon 4 (n=13 pts)	Total (n=144)
% pts with ED	83%	66.7%	15.2%	61.5%	61.1%
Median # nodes from ED	25 (4-43)	24 (4-46)	17 (3-21)	20 (8-30)	22.5 (3-46)
% pts with positive nodes after ED	18.4%	26.9%	60%	0	21.6%
Median # positive nodes after ED	2 (1-11)	3 (1-14)	1 (1-2)	0	2 (1-14)
% pts with standard dxn	17%	33.3%	84.8%	38.5%	38.9%
Median # nodes from SD	12 (4-27)	16 (7-24)	6 (0-25)	14 (4-36)	8 (0-36)
% pts with positive nodes after SD	20%	30.8%	14.3%	40%	21.4%
Median # positive nodes after SD	2	2.5 (1-3)	2.5 (2-3)	1.5 (1-2)	2 (1-3)



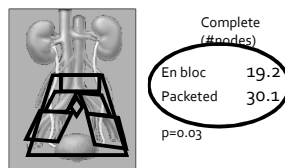
Bochner et al. J. Urol, 2004

Number of Nodes Examined Related To Method Submitted

Limited LN Dissection (N=20)



Extended LN Dissection (N=18)



Bochner et al., J. Urol, 2001

Extent of Lymphadenectomy For Invasive Bladder Cancer

Surgeon	Nodes removed (mean)	Cystectomies (n)
1	9.6	10
2	9.8	46
3	10.1	24
4	11.1	59
5	11.2	14
6	11.7	10
7	11.9	19
8	11.9	22
9	14.7	15
10	15.4	43
11	15.6	19
12	16.2	12
13	16.6	44
14	18.2	11
15	20.4	14
16	20.8	16



Leissner et al. J. Urol, 2000

Extent of Lymphadenectomy: MSKCC Prospective Study

	P value	Effect 95% CI
Surgeon	0.137	*
Pathologist	0.216	*
Neoadj chemo	0.912	-4.4 to 4.9
BCG (last 6 months)	0.082	-7.2 to 0.4
Age	0.155	-.02 to 0.0
Days from TUR to RC (continuous variable)	0.557	-.02 to 0.0
Type of dissection (extended v. standard)	<0.001	3.7 to 10.7



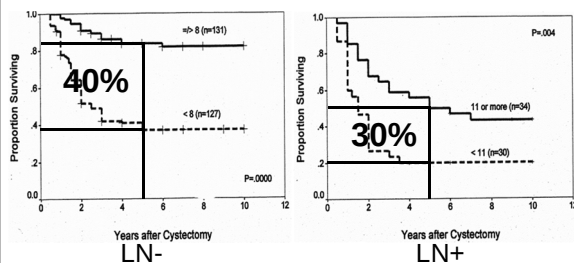
Bochner et al. J. Urol, 2004

Therapeutic Role of Lymphadenectomy in Bladder Cancer

IS MORE BETTER??



Extent of Lymphadenectomy



Herr et al, J. Urol, 2002

Differences in Treatment according to Age Adjusted Comorbidity (N=1112) MSKCC Bladder Cancer Database

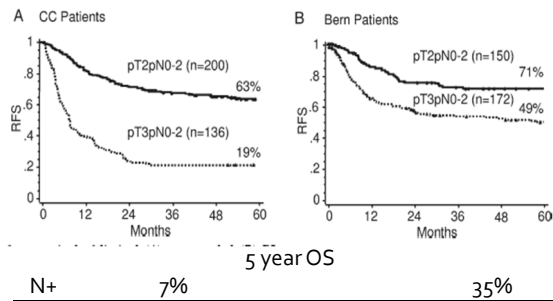
Clinical Characteristic	Age Adjusted Comorbidity			p Value
	≤2	3 to 4	≥5	
Diversion	385	654	98	<0.0005
Orthotopic	163 (42%)	114 (17%)	7 (7%)	
Continent Cutaneous	39 (10%)	28 (4%)	2 (2%)	
Conduit	183 (48%)	512 (79%)	89 (90%)	
Postoperative Chemo				0.02
No	256 (68%)	481 (75%)	75 (77%)	
Yes	121 (32%)	157 (25%)	23 (23%)	
Node Dissection Performed				0.007
No	27 (7%)	79 (12%)	17 (18%)	
Yes	358 (93%)	556 (88%)	79 (82%)	
Node Count (median)	12 (IQR 6-20)	10 (IQR 4-17)	9.5 (IQR 3.25-16)	<0.0005



Koppie et al, Cancer 2006; 107:2368-2374

Limited vs. Extended PLND

Cleveland Clinic and University of Bern



Memorial Sloan-Kettering
Cancer Center

Dhar et al, J Urol, 2008; 179:873-878

MSKCC: Radical Cystectomy Experience

Establishment of a Standard For The Lymphadenectomy

Number of nodes removed	Survival Probability at 5 years		Survival Probability at 10 years	
	Nonlinear Model	Linear Model	Nonlinear Model	Linear Model
0	38.0%	41.8%	20.6%	23.3%
4	49.6%	45.0%	29.4%	25.8%
8	50.3%	48.3%	30.0%	28.4%
12	51.1%	51.6%	30.7%	31.2%
16	53.4%	54.9%	32.7%	34.1%
20	56.5%	58.2%	35.5%	37.1%
24	60.0%	61.3%	38.9%	40.2%
32	68.0%	67.4%	47.3%	46.7%

Koppie et al, Cancer 2006; 107:2368-2374

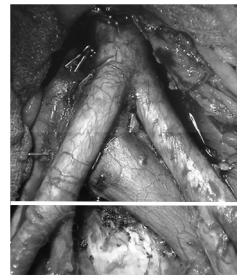
© 2017 MSKCC

Surgical Quality For Invasive Bladder Cancer

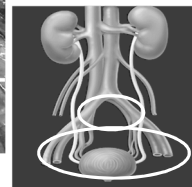
Outcome based on level of node positivity

Memorial Sloan-Kettering
Cancer Center

Bladder Cancer: PLND



Series	Total pts	Total N3 pts	5 yr RFS N1	5 yr RFS N2	5 yr RFS N3
Herlev	336	22	42%		37%
MSKCC	596	42	38%	35%	25%



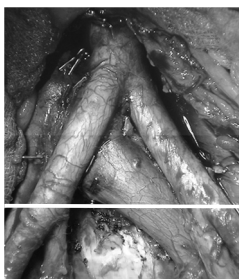
TNM Nodal Staging 2009

- N1: single positive node in primary drainage region
- N2: multiple positive nodes in primary drainage region
- N3: common iliac nodal involvement

Memorial Sloan-Kettering
Cancer Center

Tarin et al, Eur Urol, 2012
Steven and Poulsen, J Urol, 2007

Bladder Cancer: PLND



Series	Total pts	Total N3 pts	5 yr RFS N1	5 yr RFS N2	5 yr RFS N3
Herlev	336	22	42%		37%
MSKCC	596	42	38%	35%	25%

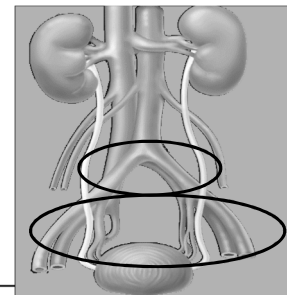
MSKCC DATA	Overall Group	≥pT2 patients
Lymph node positive	19%	34%
N3 positive group	7%	13%

Memorial Sloan-Kettering
Cancer Center

Tarin et al, Eur Urol, 2012
Steven and Poulsen, J Urol, 2007

Limited vs Extended Pelvic Lymphadenectomy In Patients With Bladder Cancer Undergoing Radical Cystectomy: Survival Results From A Prospective, Randomized Trial (LEA AUO AB25/02)

- Primary endpoint: RFS 50% vs 65% (**15% improvement**)
- 375 of 437 pts. were randomized from 02/2006 to 08/2010
- 191 limited and 184 extended PLND
- ≤ pT2 pN0 in 49.6% of patients
- 24.0% were node positive (pN+)
- median number of dissected nodes was 19 in the limited and 32 in the extended arm.

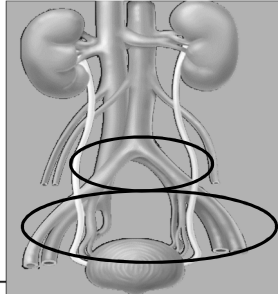


Memorial Sloan-Kettering
Cancer Center

Presented by JE. Gschwend ASCO, 2016

Limited vs Extended Pelvic Lymphadenectomy In Patients With Bladder Cancer Undergoing Radical Cystectomy: Survival Results From A Prospective, Randomized Trial (LEA AUO AB25/02)

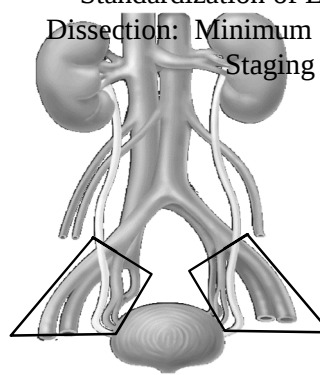
- 5-year RFS: 62.0% in the limited compared to 69.3% in the extended arm (7.3% difference)
- Hazard ratio (HR) = 0.80, 95% (CI) (0.54-1.19); log-rank p = 0.28
- 5-year CSS: 66.2% in the limited; 77.5% in the extended arm
- statistically not significant (HR = 0.70, 95%CI 0.45-1.10; log-rank p = 0.13)



Presented by JE. Gschwend ASCO, 2016



Standardization of Lymph Node Dissection: Minimum Dissection For Staging



To properly stage minimal dissection should include: EXTERNAL ILIAC, HYPOGASTRIC, OBTURATOR LYMPH NODES.

- Based on 5 anatomically based mapping studies in bladder cancer: mean number of LN range from 12-26.
- Reasonable initial recommendation would be that approximately 12 lymph nodes should be evaluated for properly performed LN dissection for STAGING.

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TREATMENT OF NON-METASTATIC MUSCLE-INVASIVE BLADDER CANCER: AUA/ASCO/ASTRO/SUO GUIDELINE

Sam S. Chang, MD, MBA, FACS; Bernard H. Bochner, MD, FACS; Roger Chou, MD; Robert Dreicer, MD, MS, MACP, FASCO; Ashish M. Kamat, MD, MBBS, FACS; Seth P. Lerner, MD, FACS; Yair Lotan, MD; Joshua J. Meeks, MD, PhD; Jeff M. Michalski, MD, MBA; Todd M. Morgan, MD; Diane Z. Quale; Jonathan E. Rosenberg, MD; Anthony L. Zietman, MD; Jeffrey M. Holzbeierlein, MD, FACS



Chang et al, J Urol, 2017

TREATMENT OF NON-METASTATIC MUSCLE-INVASIVE BLADDER CANCER: AUA/ASCO/ASTRO/SUO GUIDELINE

TREATMENT

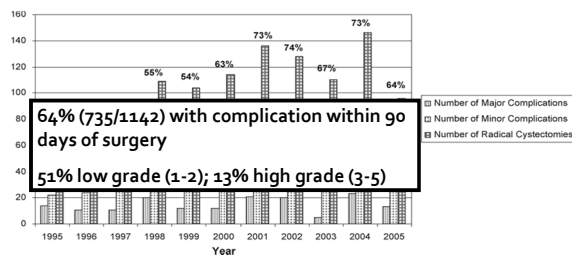
RADICAL CYSTECTOMY

- Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (Mo) muscle-invasive bladder cancer. (Strong Recommendation; Evidence Level: Grade B).
- When performing a standard radical cystectomy, clinicians should remove the bladder, prostate, and seminal vesicles in males and should remove the bladder, uterus, fallopian tubes, ovaries, and anterior vaginal wall in females. (Clinical Principle)
- Clinicians should discuss and consider sexual function preserving procedures for patients with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement. (Moderate Recommendation; Evidence Level: Grade C)



Chang et al, J Urol, 2017

Early Morbidity of Open Radical Cystectomy MSKCC 1995-2005 (n=1142)

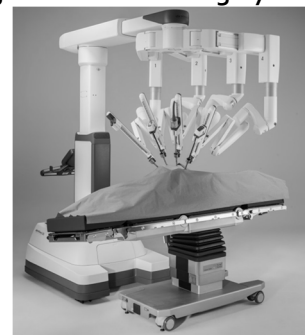


Median Age = 68 years



Shabsig et al, Eur Urol. 2008

Technological Advance In Surgery

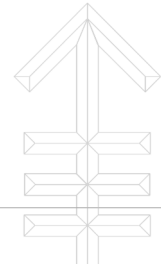


Is Robotic Cystectomy the New Standard? Establishing a New "Standard" Cancer Treatment

Oncologic	- At least achieve similar cancer specific outcomes - Improve the extent or pattern of recurrence
Complications/Recovery	- Lower complication rates - Shorten in hospital length of stay - Ease overall recovery time
Function	- At a minimum achieve similar outcomes - Allow surgeons to provide improved functional recovery
Cost	Reduce overall costs or achieve significant improvements of above to justify added costs



State Of The Evidence On Robotic Radical Cystectomy And Urinary Diversion In 2018: Complications



Systematic Review and Cumulative Analysis of Perioperative Outcomes and Complications After Robot-assisted Radical Cystectomy

Giacomo Novara^{a,*}, James W.F. Catto^b, Timothy Wilson^c, Magnus Annerstedt^d, Kevin Chan^e, Declan G. Murphy^f, Alexander Motttrie^g, James O. Peabody^h, Eila C. Skinner^h, Peter N. Wiklundⁱ, Khurshid A. Guru^{j,k}, Bertram Yuh^{c,i}

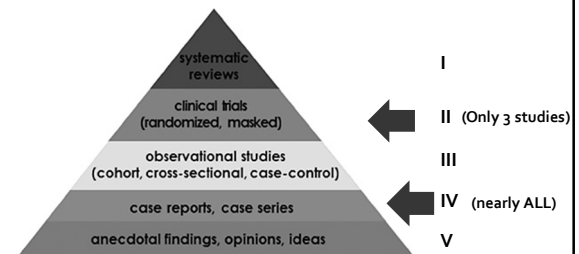


70 publications with complications data
23 reports with comparative complications data



Novara et al, European Urology, 2015

Complications Outcomes RARC Studies



RARC and Extracorporeal Diversion Complication Rates

Type of series	Number of publications	90 d complications	90 d high grade complications
RARC with Extracorporeal conduit	23	59% (30-77%)	12% (0-35%)
RARC with extracorporeal continent	6	72% (33-91%)	24% (5-37%)

Guru et al J Endo 21:2007
Hayn et al J Urol 169:2003
Guru et al J Urol 169:2007
Hemel et al J Robot Surg 2:2008
Murphy et al Eur Urol 54:2008
Park et al J Urol 169:2008
Pruthi et al Eur Urol 53:2008
Woods et al J Endo 22:2008
Gamboso et al J Robot Surg 3:2009
Kaufman et al BJU Int 105:2010

Pruthi et al J Urol 183:2010
Khan et al Urology 77:2011
Lau et al Int J Med Robot 8:2012
Smith et al J Lapendo Adv Sur Tech 22:2012
Treier et al Int Braz J Urol 38:2012
Johar et al Eur Urol 54:2013
Saar et al BJU Int 112:2012
Xylinas et al Urology 82:2013
Al-Daghmin et al Urology 83:2014
Phillips et al J Endo 28:2014

Kang et al J Endo 24:2010
Snow-Lisy et al Eur Urol 65:2014
Kwan et al Korean J Urol 15:2014
Josephson et al Int J Med Robot 6:2010
Karaeian et al J Endo 24:2010
Torrey et al Urology 79:2012
Yuh et al Eur Urol 62:2012
Nazmy et al J Urol 194:2014
Yuh et al J Endo 28:2014



Adapted from Novara et al Eur Urol 2015



MSKCC: A Prospective, Randomized Phase III Trial Comparing 90 Day Complications Robotic versus Open Radical Cystectomy



MSKCC RARC vs ORC: Methodology

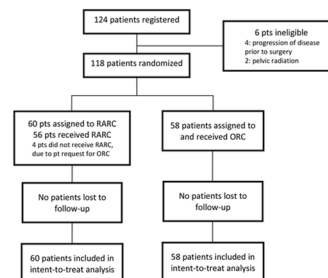
Expertise Trial Design: high volume surgeons with extensive robotic and open experience included

All RARC patients operated by experienced robotic surgeons, all open patients operated by open surgeons (open surgeons completing all diversions open)

All patients managed on identical standardized post operative pathway (4-5d discharge possible)



Bochner et al, N Engl J Med, 371:389-90, 2014
Bochner et al Eur Urol, 2014, <http://dx.doi.org/10.1016/j.eururo.2014.11.043>

RARC vs ORC: Randomization and Treatment Groups

Bochner et al, N Engl J Med, 371:389-90, 2014
Bochner et al Eur Urol, 2014

Primary Outcome: 90 day Complications

Outcome	Robotic (N=60)	Open (N=58)	Difference (95% CI)	p-value
% Patients Grade 2-5	62%	66%	-3.9% (-21%, 13%)	0.7
% Patients Grade 3-5	22%	21%	1.0% (-14%, 16%)	0.9
Length of Hos. Stay (days)	8	8	0 (-2, 1)	0.9



Bochner et al, N Engl J Med, 371:389-90, 2014
Bochner et al Eur Urol, 2014, <http://dx.doi.org/10.1016/j.eururo.2014.11.043>

RARC vs ORC: Surgical and Pathologic Details

	Robotic	Open	Difference	P value
Blood Loss (ml)	500	681	-181 (-321, -41)	0.012
Operative Time (min)	464	330	134 (106, 162)	<0.0001
Length of Hos. Stay (days)	8	8	0 (-2, 1)	0.9



Bochner et al, N Engl J Med, 371:389-90, 2014
Bochner et al Eur Urol, 2014, <http://dx.doi.org/10.1016/j.eururo.2014.11.043>

MSKCC Prospective, Randomized Trial Comparing RARC and ORC Conclusions

- RARC appears comparable to ORC in terms of safety with similar complication rates
- RARC leads to lower blood loss and transfusion requirements at the cost of longer OR times
- RARC and ORC can provide similar pathologic outcomes including margin rates and LN yields
- There does not appear to be an advantage of RARC over ORC**



Bochner et al, N Engl J Med, 371:389-90, 2014
Bochner et al Eur Urol, 2014, <http://dx.doi.org/10.1016/j.eururo.2014.11.043>

RARC and INTRACORPOREAL Diversion Complication Rates

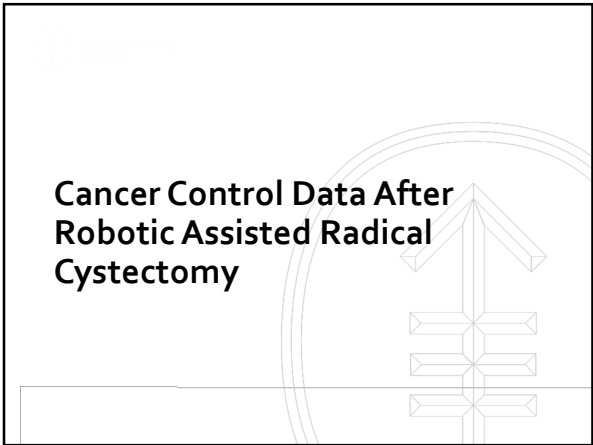
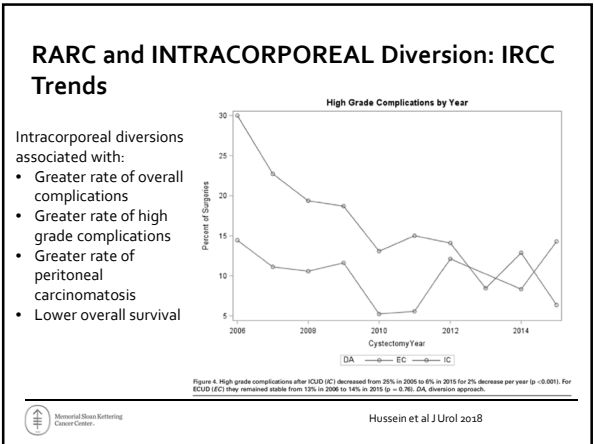
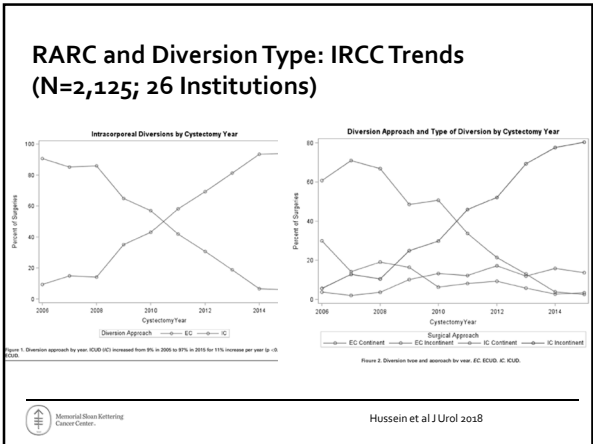
Type of series	Number of publications	90 d complications	90 d high grade complications
RARC with intracorporeal conduit	6	72% (58-86%)	Up to 90D 25% (13-56%)
RARC with intracorporeal continent	6	76%	30 d: 28% 30-90 d: 18% reop: 33%

Pruthi et al Eur Urol 57:2010
Goh et al Eur Urol 62:2012
Bishop et al Adv Urol 2013
Schumacher et al Urology 77:2011
Canda et al BJU Int 110:2012

Jonsson et al Eur Urol 60:2011
Azzouzi et al Eur Urol 63:2013
Collins et al Eur Urol 64:2013
Akbulut et al J Endo 25:2011



Adapted from Novara et al Eur Urol 2015



RARC Cancer Outcomes: Stage and Follow Up

Institution	Number of pts	≤T2	>T2	Follow up (months)
UNC	50	66	34	13
Multicenter	104	70	30	12
Cornell	85	64	36	18
Mayo/Tulane	59	47	53	21
UNC	100	67	33	21
Saarland Univ	91	67	33	15
Karolinska Univ	113	75	25	25
Cornell	175	65	35	37
City of Hope	162	67	33	52
Roswell Park	99	48	52	74

Pruthi et al Urology 72, 2008
Kauffman et al BJU Int 107, 2011
Tremp et al Int Braz Urol 46, 2013
Raza et al Eur Urol 66, 2014

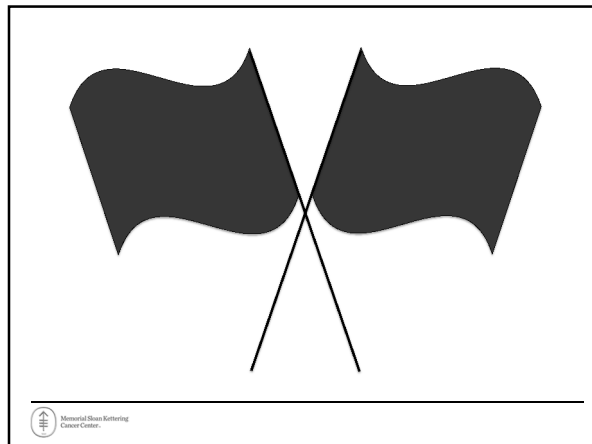
Yuh et al J Endourol 28, 2014
Martin et al BJU Int 109, 2010
Collins et al Eur Urol 64, 2013

Kang et al J Endourol 24, 2010
Pruthi et al J Urol 183, 2010
Xylinas et al Urology 84, 2013

ORC Cancer Outcomes: Stage and Follow Up

institution	Number of pts	≤T2	>T2	Follow up (months)
USC	1054	51	49	122
MKSCC	1121	52	48	36

Stein et al JCO 2003, 19:666-675
Koppie et al Eur Urol 2008, 112:2384-92



Recurrence Patterns After Open and Robot-assisted Radical Cystectomy for Bladder Cancer

Daniel P. Nguyen^{a,b,*}, Bashir Al Hussein Al Awamlh^a, Xian Wu^c, Padraic O'Malley^a, Igor M. Inoyatov^a, Abimbola Ayangbesan^a, Bishoy M. Faltas^d, Paul J. Christos^c, Douglas S. Scherr^a

^aDepartment of Urology, Weill Cornell Medical College-New York Presbyterian Hospital, New York, NY, USA; ^bDepartment of Urology, Bern University Hospital, Bern, Switzerland; ^cDepartment of Healthcare Policy and Research, Division of Biostatistics and Epidemiology, Weill Cornell Medical College, New York, NY, USA; ^dDepartment of Medicine, Division of Hematology/Medical Oncology, Weill Cornell Medical College-New York Presbyterian Hospital, New York, NY, USA

Surgical Technique	#pts	Any recurrence	Local recurrence	Distant recurrence	Extrapelvic lymph node recurrences	Peritoneal Carcinomatosis
Open	120	42%	23% (43/73)	36%	15%	2/73 (2.7%)
RARC	263	36%	18% (15/147)	29%	23%	9/147 (6.1%)



Nguyen et al, Eur Urol 2015

MSKCC Prospective, Randomized Trial Comparing RARC and ORC

Following RARC

- Non-statistically significant trend for lower metastatic sites HR 2.21 (p=0.06)
- Higher risk for abdominal/pelvic recurrences HR2.93 (p=0.035)

Any Recurrence (#patients)	Robotic (N=60)	Open (N=58)
Local Recurrence (p=0.077)		
Rectum	3	0
Pelvic Lymph Nodes	6	2
Pelvic Soft Tissue	8	3
Abdominal Recurrence (p=0.2)		
Abdominal Wall	5	0
Bowel	5	1
Peritoneum (Carcinomatosis)	2	2
Soft Tissue	2	1
Distant Recurrence (p=0.064)		
Adrenal	0	1
Bone	2	3
Extra-pelvic Lymph Nodes	5	10
Liver	2	4
Lung	1	9
Soft Tissue	2	3
Urothelial Recurrence		
Upper Tract	5	3
Urethra	1	2



Early Recurrence Patterns Following Totally Intracorporeal Robot-assisted Radical Cystectomy: Results from the EAU Robotic Urology Section (ERUS) Scientific Working Group

In 717 patients treated by RARC

Low rate of peritoneal carcinomatosis 0.7%

Pelvic recurrence rate of 10.7%

	Estimated recurrence rate (%)		
	3 mo	12 mo	24 mo
Any recurrence	4.1	19.8	25.4
Local recurrence	1.8	8.2	10.7
Cystectomy bed	0.7	2.8	3.4
Distal ureteric	0.1	0.3	0.5
Urethral	0.0	0.1	0.5
Pelvic lymph nodes	1.0	5.3	7.2
Distant recurrences	3.0	13.9	17.8
Lung	1.1	4.6	6.2
Liver	0.8	4.1	5.5
Bone	1.0	5.2	6.4
Brain	0.1	0.6	1.0
Adrenal	0.0	0.3	0.7
Bowel	0.0	0.3	0.3
Pancreas	0.0	0.1	0.1
Extrapelvic lymph nodes	1.4	4.9	6.6
Peritoneal carcinomatosis	0.3	0.7	0.7
Port site	0.0	0.3	0.3
Skin	0.0	0.1	0.1
Muscle	0.0	0.2	0.2
Secondary urothelial cancer			
Upper urinary tract	0.0	0.3	0.3
Multiple recurrences	2.0	8.0	11.0



Collins et al Eur Urol, 2016

Introduce Surgical Improvements for RC Establishing a new "Standard"

Oncologic	• Selection of early stage disease • Short follow up • Lack of information on patterns of recurrence
Complications/Recovery	• No difference in complications • No improvement in length of stay • Open, extracorporeal, intracorporeal
Function	• Data is so limited that NO conclusions can be drawn
Cost	• ??



MSKCC Randomized RARC vs ORC: Treatment Costs

Treatment Arm and urinary diversion	Patients (N)	Average total cost \$	95% CI (log \$)	p value
Neobladder Robotic	30	19,231.26	9.77-9.92	
Neobladder open	35	15,311.00	9.54-9.69	
Difference		3,920.26	0.13-0.33	P<0.0001
Ileal conduit robotic	26	18,388.19	9.72-9.87	
Ileal conduit open	24	16,648.58	9.50-9.79	
Difference		1,739.61	0.001-0.317	P<0.05



Bochner et al Eur Urol, 2014

Have we established a new
standard for the surgical
treatment bladder cancer?
NO

Have we established a new
~~standard~~ option for the
surgical treatment bladder
cancer?
Yes, but...



Bladder-Preserving Trimodality Therapy for Management of Muscle Invasive Bladder Cancer

Jason A. Efstathiou, MD, DPhil
Associate Professor, Harvard Medical School
Director, Genitourinary Division, Department of Radiation Oncology
Clinical Co-Director, Bertucci Center for Genitourinary Cancers
Massachusetts General Hospital
Boston, MA





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Disclosures

Reports no relationships with a commercial interest





Session Learning Objectives

- Review prospective randomized trials and large institutional experiences utilizing tri-modality therapy for muscularis propria invasive bladder cancer
- Discuss which patients are candidates for tri-modal bladder sparing therapy, and which patients are not candidates and should instead undergo radical cystectomy
- Describe the technique and importance of aggressive initial transurethral resection, repeat transurethral resection and ongoing cystoscopic surveillance of the bladder
- Describe the coordinated multidisciplinary technique in tri-modality therapy, including radiosensitizing chemotherapy agents, radiation, and adjuvant chemotherapy
- Describe the indications for salvage cystectomy, discuss management of noninvasive recurrences, and understand the quality of life and potential toxicities after tri-modal therapy





Agenda

- Rationale for bladder sparing tri-modal therapy
- Patient selection for TMT vs. radical cystectomy
- Importance of coordinated multi-disciplinary care
- Critical role of aggressive TURBT and repeat TURBT
- TMT paradigm and outcomes
- Chemotherapy options and delivery with TMT
- Surveillance, follow-up and addressing recurrences after TMT: NMIBC and MIBC
- Quality of life, predictive biomarkers and future advances





Rationale for bladder sparing tri-modal therapy

Organ conservation by tri-modality therapy (TMT) is commonplace in contemporary oncology

- Laryngeal carcinoma
- Anal carcinoma
- Breast carcinoma
- Esophageal carcinoma
- Limb sarcomas

In primary muscle-invasive bladder cancer (MIBC), radical cystectomy remains the most commonly offered treatment

There are no completed randomized trials comparing bladder-preserving TMT with radical cystectomy

While most patients do well, it is a major physiologically challenging surgery and can be life altering





Complications of radical cystectomy

Defining Early Morbidity of Radical Cystectomy for Patients with Bladder Cancer Using a Standardized Reporting Methodology

Ahmad Shabir¹, Ruslan Korde², Kirpal C Vora³, Christine M. Briggs⁴, Angel M. Quinn⁵, Caroline Savage⁶, Ganesh Raj⁷, Bernard H. Bodine⁸, Guido Dalbagni⁹, Harry W. Herr¹, S. Madhele Donat¹⁰

European urology 53 (2008) 164–170

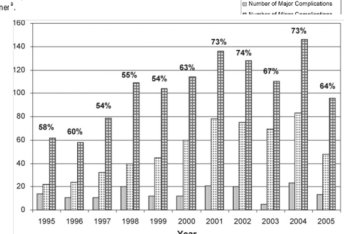


64% of patients experienced a complication within 90 days

13% had high-grade (Clavien 3-5) complication

26% readmission rate

2.7% 90 day mortality



Year	Number of Major Complications
1995	58%
1996	60%
1997	64%
1998	65%
1999	64%
2000	63%
2001	73%
2002	74%
2003	67%
2004	73%
2005	64%

Contemporary Cystectomy

Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial

Bernard H. Bochner^{a,*}, Guido Dalbagni^a, Daniel D. Sjoberg^b, Jonathan Silberstein^{a,d}, Gal E. Keren Paz^c, S. Machele Donat^a, Jonathan A. Coleman^a, Sheila Mathew^a, Andrew Vickers^d, Geoffrey C. Schnorr^d, Michael A. Feuerstein^a, Bruce Rapkin^a, Raul O. Parra^a, Harry W. Herr^a, Vincent P. Laudone^a

- ~2/3 of patients had Clavien 2-5 complications by 90 days
- No difference in 90 day complications, hospital stay, and 3- and 6-month QOL outcomes

Table 3 – Complication types observed by randomization arm

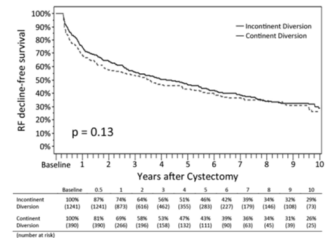
	Robotic (<i>n</i> = 60)	Open (<i>n</i> = 58)	Difference, <i>S</i>	95% CI for difference, <i>S</i>	<i>p</i> value
Reading	3 (5.0)	3 (5.2)	0.2	-8 to 8	>0.9
Cartak	9 (15)	8 (14)	-1.2	-13 to 10	0.9
Cartoonist	14 (23)	17 (29)	3	-22 to 28	0.5
Contemporary	3 (5.0)	8 (14)	5	-19 to 17	0.16
Electrics	21 (36)	17 (29)	-4	13 to 25	0.1
Miscellaneous	2 (3.3)	2 (3.5)	-1.8	-9 to 5	0.0
Newsprint	5 (8.3)	2 (3.4)	-4.9	-15 to 13	0.1
Primary	13 (22)	17 (29)	4	-10 to 18	0.1
Target	0 (0.0)	1 (1.7)	1.7	-5 to 8	0.1
Technoscientific	3 (5.0)	5 (8.6)	-0.3	-10 to 10	>0.9
Total	2 (3.3)	8 (14)	10	20 to 0	<0.001

Cl

Renal Insufficiency with Cystectomy

Long-Term Renal Function Outcomes after Radical Cystectomy

Manuel S. Eisenberg, R. Houston Thompson, Igor Frank,* Simon P. Kim,
Katherine J. Cotter, Matthew K. Tollefson, Dharam Kaushik, Prabin Thapa,
Robert Tarrell and Stephen A. Boorjian†



- Decline in GFR defined as >10 ml per minute/1.73m²
- ~72% had decrease in GFR by 10 yrs
- ~56% new onset Stage 3 CKD
- 3.5% progress to hemodialysis

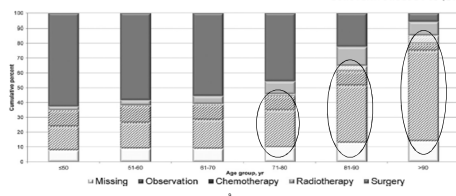
Undertreatment of MIBC in an aging population

With advances in health care and the aging population more patients are living longer

Use of Potentially Curative Therapies for Muscle-invasive Bladder Cancer in the United States: Results from the National Cancer Data Base

Phillip J. Gray^{a,b}, Stacey A. Fedewa^c, William U. Shipley^{a,*}, Jason A. Efstathiou^a, Chun-Chieh Lin^c, Anthony J. Zietman^a, Katherine S. Mince^d

EUROPEAN UROLOGY 63 (2013) 823–829



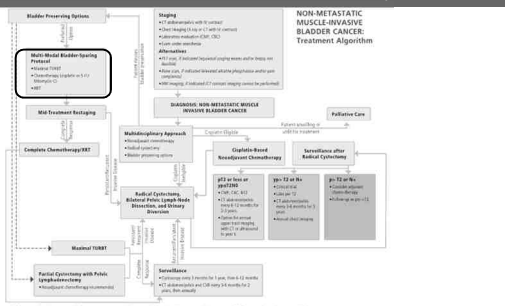
Options for management of MIBC

Radical Cystectomy +/- perioperative chemotherapy

Bladder preservation therapy

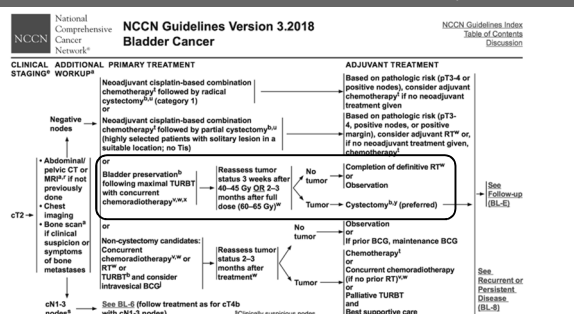
- Maximal TUR combined with chemoradiation
- Partial cystectomy
- TURBT +/- chemotherapy

AUA Guidelines

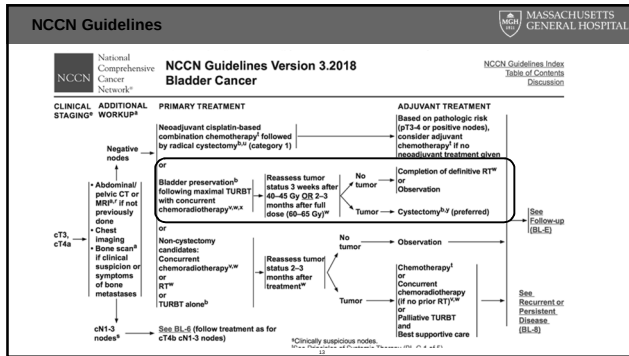


(Chl) complete leafy shoot; (Chf) companion particle agar; (Chd) third ring or palisade stage; 5,000×transverse section of blade; tery

NCCN Guidelines



cN1-3 nodes^a → See BL-6 (follow treatment as for cT4b with cN1-3 nodes) ^aClinically suspicious node



TMT supported by advocacy groups

Urology Care FOUNDATION Muscle Invasive Bladder Cancer: A Patient Guide

GET TREATED

What are my options for MIBC treatment?

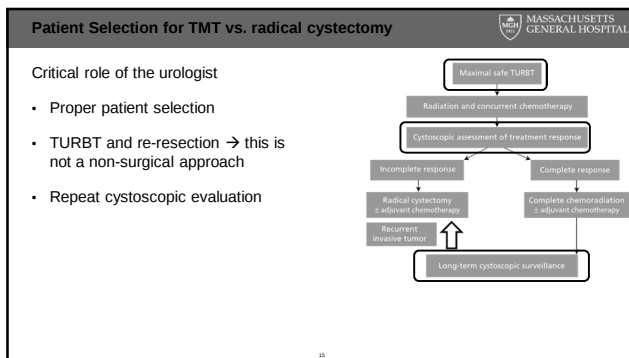
PARTIAL CYSTECTOMY

CHEMOTHERAPY WITH RADIATION

RADICAL CYSTECTOMY

Bladder Cancer Advocacy Network (BCAN)

"Bladder preservation with chemotherapy and radiation is suitable for those who meet the specific requirements"



Patient Selection for TMT vs. radical cystectomy

Tumor factors (cautions):

- Inability to achieve a complete resection (ie. Clinical T3b-4 disease)
- Presence of hydronephrosis
- Large tumor burden involving majority of bladder
- Extensive CIS
- High grade tumor in bladder diverticulum
- Upper tract involvement of tumor
- Prostatic involvement:
 - Prostatic stromal invasion
 - CIS prostatic urethra
- Extensive bladder neck involvement in women

Imaging: MRI, CT, Ultrasound.

Patient Selection for TMT vs. radical cystectomy

Tumor factors:

- Not every case needs to be perfect
- Can have some adjacent CIS
- Can have (limited) satellite non-muscle invasive tumors
- It's the size of the wall involvement (stalk), not the size of the tumor

Imaging: MRI, CT, Ultrasound.

Patient Selection for TMT vs. radical cystectomy

Patient factors:

- Ability to tolerate concurrent radiosensitizing chemotherapy
- Poor candidate for radiation therapy
 - Prior pelvic radiation
 - Inflammatory bowel disease
 - Poor baseline bowel function
 - Poor baseline bladder function

Importance of multidisciplinary care

Critical role of coordinated care:

- Communicating information about tumor location and resection
- Coordinating chemotherapy, radiation, repeat cystoscopic evaluations in a timely fashion
- Communication of tumor location and details about TURBT

Contemporary Patterns of Multidisciplinary Care in Patients With Muscle-invasive Bladder Cancer

Lauren C. Hardman,¹ Abhishek Tripathi,¹ Matthew Kuo,² Jason A. Efstathiou,¹ Andrea B. Apala,³ Jean H. Hoffman-Censits,³ Walter M. Stadler,⁴ Evan Y. Yu,¹ Ronald H. Beckman,⁵ Ella C. Skinner,⁶ Tracy Quinlan,⁷ Anne E. Kille,¹ Dean F. Bajorath,⁸ Khurshid Gani,⁹ William L. Shipley,¹ Gary D. Stonberg,⁸ Noah M. Hahn,¹⁰ Srikala S. Sridhar¹⁴

Clinical Genitourinary Cancer, Vol. 15, No. 1, p. 1-10, 2017

• Most academic centers use multi-disciplinary care in bladder cancer

Variable	Existing Multidisciplinary Model (%)	Preferred Multidisciplinary Model (%)
Sequential, with same day appointments among different specialties	39	41
Sequential, with different day appointments among different specialties	57	15
Coordinated, one-time visit with multiple physicians (seeing patient at once)	22	26
Concurrent consults	19	0
E-mail consults	14	0
None	5	2

A. TUMOR LOCATION BEFORE TURBT

B. POST-TURBT: IF MACROSCOPIC TUMOR REMAINS AT END OF PROCEDURE, INDICATE ITS LOCATION. IF NOT, CHECK NONE.

TURBT in TMT

Importance and technical considerations

MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

TURBT – One of the keys to success of TMT

Maximal Complete TURBT

Number at risk:
TURBT complete: 332, 301, 263, 221, 194, 165, 143, 124, 109, 97, 76
TURBT incomplete: 138, 120, 88, 78, 63, 55, 43, 40, 36, 33, 29

Corroborated by other centers:

- Rodel, et al. JCO, 2002
- Zapatero, et al. Urol Oncol, 2010
- Perdoni, et al. Cancer, 2008

Giacalone et al. Eur Urol 2017

The TURBT in TMT – this is very much a surgical approach!

TURBT goal → Remove all visible tumor; not just prove muscle invasion!

Bimanual examination under anesthesia:

- Assess for fixation, induration, mass

Technical considerations:

- Best under general anesthesia
- May need neuromuscular blockade to prevent obturator spasm
- Bipolar resection may be preferred
- NBI or hexaminolevulenic acid with blue light an option to aid resection
- Manual suprapubic pressure to manipulate anterior or lateral bladder wall

The TURBT in TMT – this is very much a surgical approach!

Partial distension of the bladder can avoid wall thinning and risk of perforation
Beware of thinner bladder wall in women (particularly elderly)
TURBT is aggressive for complete resection

- Deep resection of all visible tumor
- May resect into bladder neck and prostatic urethra if needed
- May resect ureteral orifice and part of tunnel if needed → leave stent through entire course of radiation

Repeat TURBT

ALWAYS perform repeat TURBT for cases of MIBC that have been resected elsewhere

- YOU must be comfortable that all tumor has been resected and that the patient is truly a candidate for TMT

If YOU performed initial TURBT, can occasionally avoid repeat TURBT only if satisfied that you have resected and fulgurated everything, but complete resection and fulguration of any associated urothelial disease is key

Cystoscopic reassessment after induction chemoRT

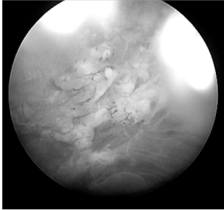
Cystoscopy and re-TURBT of tumor site is performed can be performed post-induction

This is the opportunity to assure no residual disease

Must assess entire bladder mucosa and muscularis of primary tumor site

Debride fibrinous eschar with cold loop and then biopsy/resect viable tissue in bladder wall

Don't necessarily always re-resect the entire site



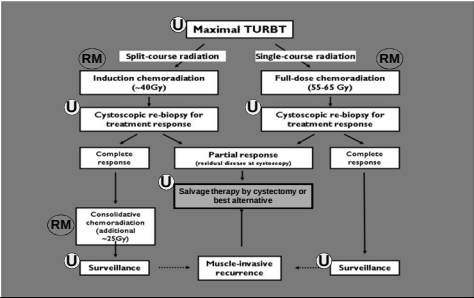
TMT Paradigm & Outcomes



MASSACHUSETTS
GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Two Standard CRT Methods of Bladder Preservation for MIBC



Bladder Conservation: Evolution of the MGH and NRG/RTOG approach

1986-93	1994-98	1999-2018
Neoadjuvant chemo	Accelerated radiation	Enhanced Radiation sensitization
Response evaluation	Adjuvant chemotherapy	Adjuvant chemotherapy
MCVx2 ↓ RT + C	bidRT+C/5FU ↓ MCV x 3	bidRT+C/5FU or C/Tax qdRT+Gem or 5FU/MMC ↓ G + C x 4

Long-term results of TMT are excellent and comparable to RC
MGH Experience 1986-2013 (cT2-T4, n=475, f/u 7.2yrs)

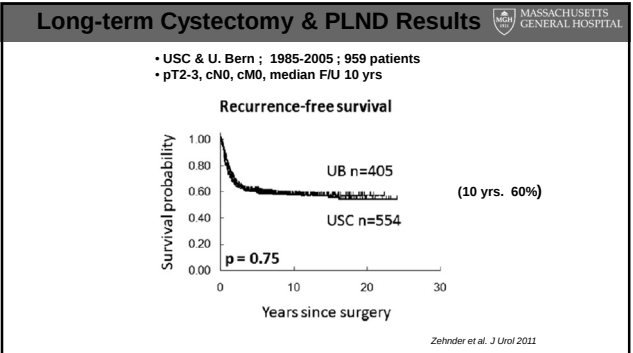
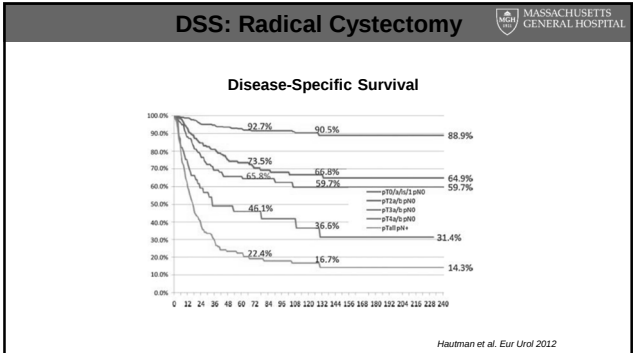
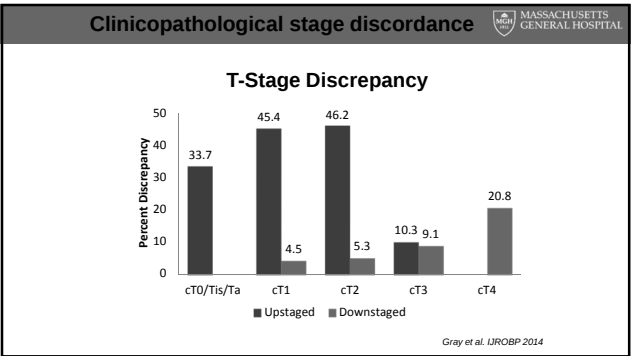
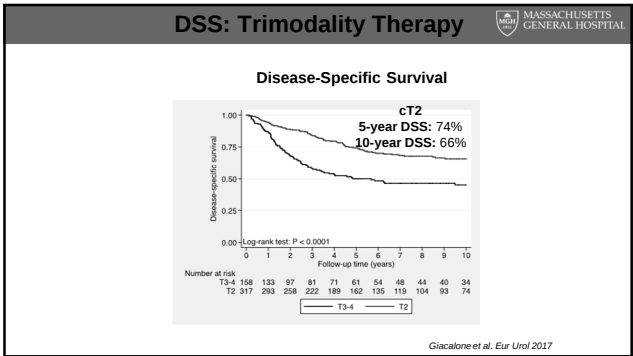
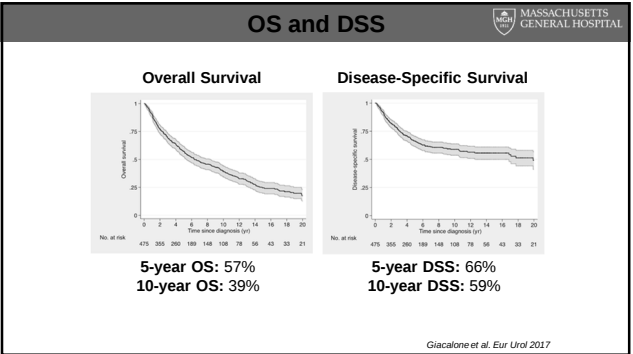
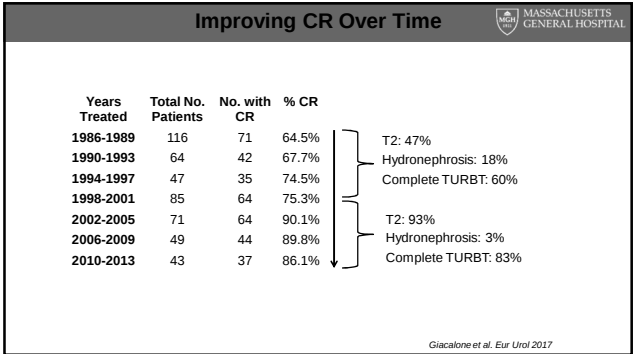
	n	%
Median Age	67	
Sex		
Male	357	75%
Female	118	25%
Clinical T Stage		
cT2	317	66%
cT3	134	29%
cT4a	24	5%
Hydronephrosis	57	12%
Carcinoma in situ	116	24%

Giacalone et al. Eur Urol 2017

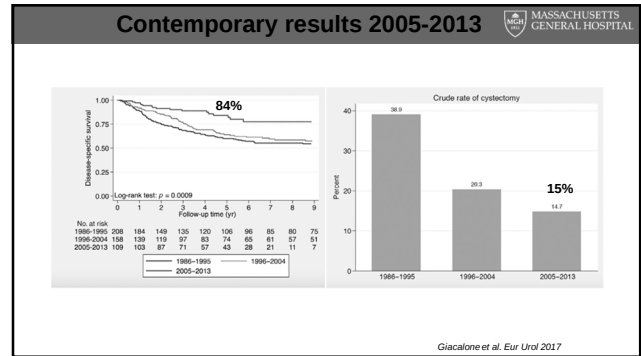
Long-term results of TMT are excellent and comparable to RC
MGH Experience 1986-2013 (cT2-T4, n=475, f/u 7.2yrs)

	n	%
Neoadjuvant Chemotherapy	118	25%
TURBT		
Visibly complete	333	70%
Visibly incomplete	142	29%
Response to induction chemoradiation		
Complete	357	75%
Incomplete	110	23%
Unknown	8	2%

Giacalone et al. Eur Urol 2017



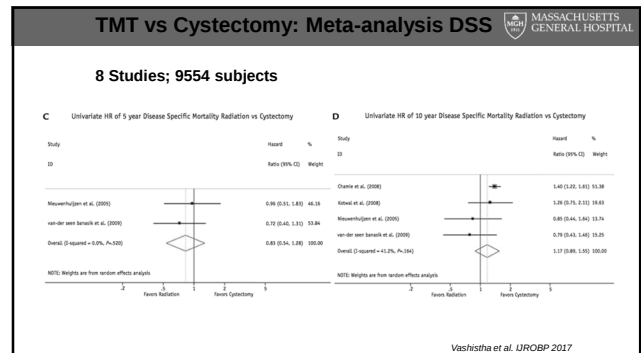
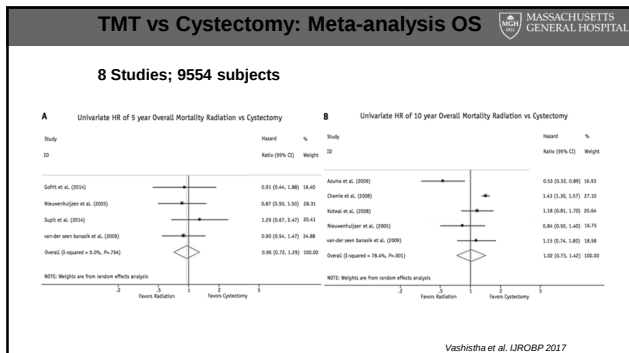
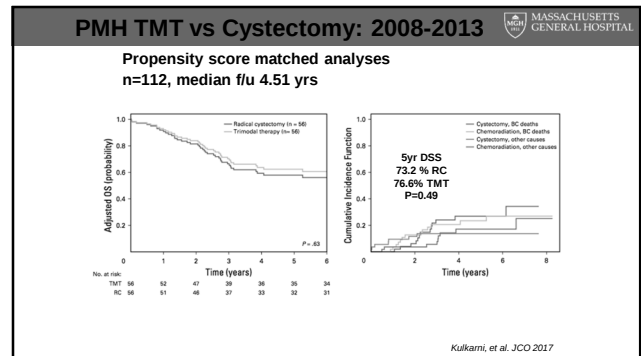
Survival after curative therapy					
	Stage	Number	5 year OS	10 year OS	
Cystectomy USC 2001	pT2-4a	633	48%	32%	
MSKCC 2001	pT2-4a	181	36%	27%	
SWOG 2003	cT2-3	303	49%	-	
Chemo-RT RTOG 1998	cT2-4a	123	49%	-	
Erlangen 2002	cT2-4	326	45%	29%	
MGH 2017	cT2-4a	348	57%	39%	
BC2001 2012	cT2-4a	182	48%	-	
RTOG pooled 2014	cT2-4a	468	57%	36%	

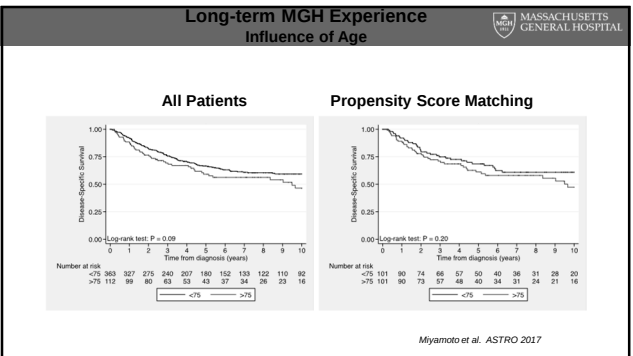
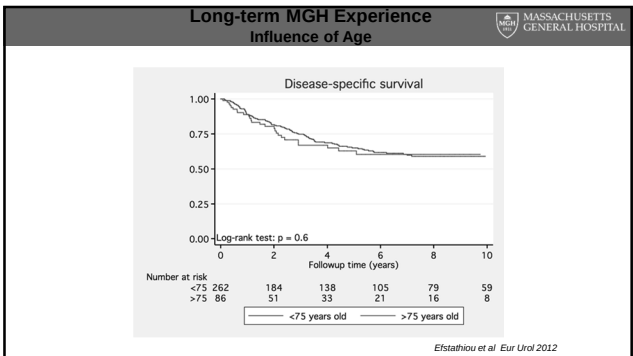
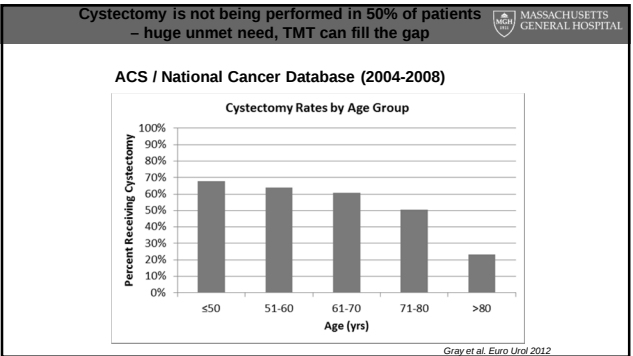
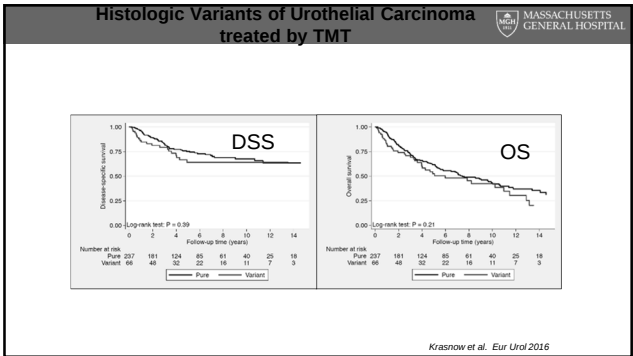


Multivariate Cox Regression Analyses

Covariates	Comparison	Overall survival			Disease-specific survival			Bladder-intact disease-specific survival		
		HR	p value	95% CI	HR	p value	95% CI	HR	p value	95% CI
Age at diagnosis	Continuous	1.03	<0.001	1.01-1.04	—	—	—	—	—	—
Clinical T stage	T2 vs T3/T4a	0.57	<0.001	0.44-0.75	0.51	<0.001	0.36-0.73	—	—	—
Response to chemoradiation	Complete vs incomplete	0.61	0.001	0.46-0.81	0.49	<0.001	0.34-0.71	0.16	<0.001	0.12-0.21
Hydronephrosis	Presence vs absence	1.51	0.02	1.06-2.15	—	—	—	1.89	<0.001	1.33-2.63
Tumor-associated CIS	Presence vs absence	1.56	0.002	1.17-2.08	1.50	0.03	1.03-2.17	—	—	—
TURBT	Complete vs incomplete	—	—	—	—	—	—	0.72	0.02	0.55-0.96

Giacalone et al. Eur Urol 2017





Chemotherapy in TMT

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Concurrent chemotherapy is important to the success of TMT

MASSACHUSETTS GENERAL HOSPITAL

Key roles for chemo in TMT

- Concurrent chemotherapy with radiation
- Adjuvant chemotherapy
- Neoadjuvant chemotherapy

Active radiosensitizing drugs

- Cisplatin
- Paclitaxel
- 5-FU
- Mitomycin C
- Gemcitabine (low dose)
- Carbogen/nicotinamide

Which chemotherapy agent should we choose?

Erlangen Experience

	n	CR
RT alone	98	57%
RT + carboplatin	69	64%
RT + cisplatin	115	81%
RT + 5-FU/cisplatin	45	87%

Rodel et al. UROBP 2002; S2: 1303-1309.

A few highlighted studies

BC2001: QD RT + mitomycin-C + 5FU vs. QD RT

RTOG 0233: BID RT + 5FU + cisplatin vs. BID RT + paclitaxel + cisplatin; both arms get adjuvant cisplatin / paclitaxel / gemcitabine

University of Michigan: QD RT + gemcitabine

RTOG 0712: BID RT + 5FU + cisplatin vs. QD RT + gemcitabine; both arms get adjuvant cisplatin / gemcitabine

BC2001

Phase 3 of chemoRT vs RT alone in muscle-invasive bladder cancer

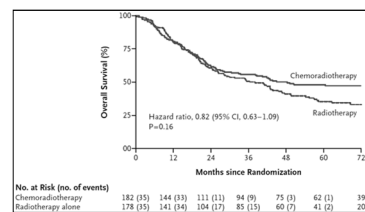
- 360 patients (accrued 2001 – 2008)
- clinical stage T2-4aNx bladder cancer
- XRT 55 Gy/20 or 64 Gy/32
- RT ± MMC & 5-FU → MMC: 12mg/m² on d1
5FU: 500mg/m²/d IVCI on d1-5, d16-20
- GFR > 25 mL/min
- Median follow-up 69.9 months
- Primary endpoint: survival free of locoregional disease
- Secondary endpoints: overall survival, toxic effects

Disadvantage:
Port-a-cath

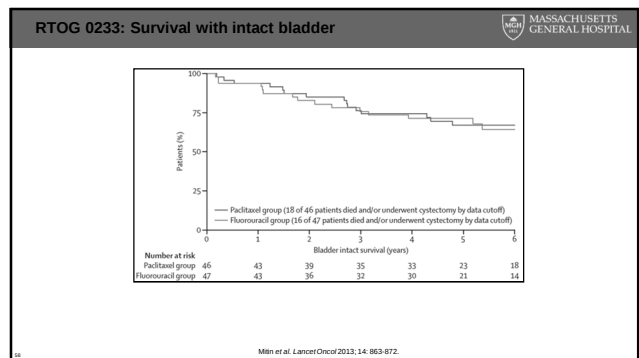
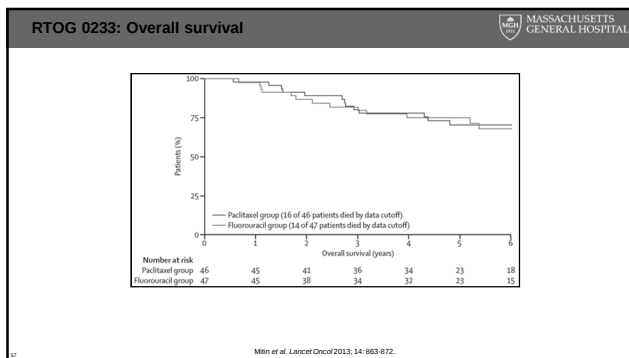
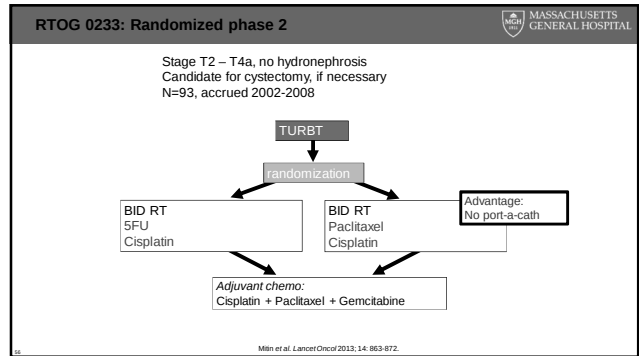
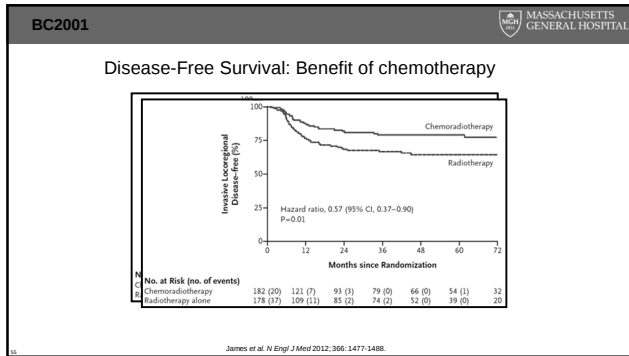
James et al. N Engl J Med 2012; 366: 1477-1488.

BC2001

Overall Survival: Benefit of chemotherapy



James et al. N Engl J Med 2012; 366: 1477-1488.



RTOG 0233: Generally similar toxicity

	Paclitaxel group (n=46)			Fluorouracil group (n=47)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Allergic or immunologic	1	0	0	0	0	0
Auditory or hearing	0	0	0	0	0	0
Blood or bone marrow	21	7	5	18	7	3
Cardiovascular (any/overall)	0	0	0	0	1	1
Cardiovascular (general)	5	0	0	2	0	0
Constitutional symptoms	23	4	0	19	8	1
Dermatological or skin	7	2	0	4	2	0
Gastrointestinal	25	10	0	1	27	12
Hemorrhage	2	1	0	2	4	0
Hepatic	10	3	1	0	9	1
Infected or infection	0	0	0	0	1	0
Integumentary	13	0	5	3	11	0
Musculoskeletal	0	0	0	0	1	0
Neurologic	6	0	1	0	8	1
Other	0	0	0	1	0	0
Pain	7	2	0	7	3	0
Pulmonary	1	1	0	2	1	0
Renal or genitourinary	15	0	4	0	18	2
Sexual or reproductive function	0	1	0	0	1	0

No grade 1 toxic effects were reported. Patients could report <1 adverse event (graded according to Common Terminology Criteria for Adverse Events, version 3.0).

Table 2. Toxic effects associated with induction chemotherapy and radiotherapy

	Paclitaxel group (n=46)			Fluorouracil group (n=47)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Blood or bone marrow	19	13	3	0	24	6
Cardiovascular (general)	1	0	0	0	0	0
Constitutional	21	9	0	0	23	3
Symptoms	11	1	0	3	0	1
Endocrine	1	0	0	0	0	0
Gastrointestinal	13	12	0	0	21	5
Hemorrhage	3	0	0	0	0	0
Impacts	10	2	0	0	3	0
Infected or infection	1	1	0	0	0	2
Integumentary	0	1	0	0	0	0
Lymphatic or laboratory	9	7	8	1	12	6
Musculoskeletal	1	0	0	2	1	0
Neurologic	9	4	0	3	7	0
Other	0	0	0	2	0	0
Pain	7	2	0	0	4	0
Pulmonary	3	1	0	0	1	0
Renal or genitourinary	20	8	0	0	15	6
Sexual or reproductive function	1	0	0	0	0	1

No grade 1 toxic effects were reported. Patients could report <1 adverse event (graded according to Common Terminology Criteria for Adverse Events, version 3.0).

Table 3. Toxic effects associated with consolidation chemotherapy and radiotherapy

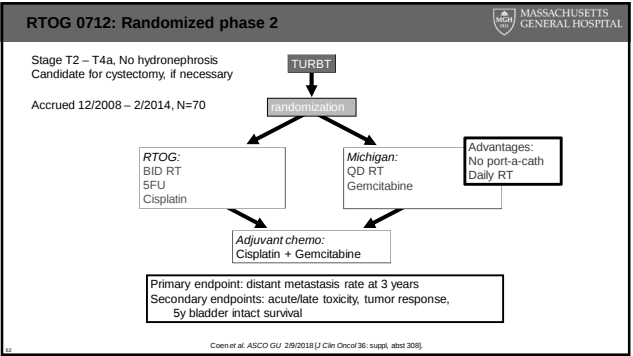
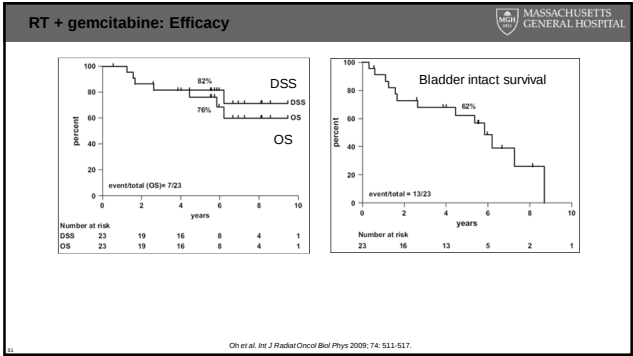
University of Michigan studies

Phase 1 daily RT and twice-weekly gemcitabine

- 23 evaluable patients; candidates for cystectomy if necessary
- clinical stage T2-3Nx bladder cancer
- XRT 60 Gy/6 weeks
- RT + BIW gemcitabine
- Creatinine ≤ 2.0
- Median follow-up 5.6 years

Gem dose (N)	Max tolerated dose
10mg/m ² (3)	316 DLTs (DVT, UTI, LF Ts)
20mg/m ² (6)	2/3 DLTs (edema, diarrhea)
30mg/m ² (6)	
33mg/m ² (3)	

Kerr et al. *J Clin Oncol* 2004; 22: 2540-2545.
Ch et al. *Int J Radiat Oncol Biol Phys* 2009; 74: S11-S17.



RTOG 0712: Primary endpoint

Distant Metastasis at Three Year Follow-up on Evaluable Patients

	5 Fluorouracil and Cisplatin + BID Irradiation (n=27*)	Gemcitabine + QD Irradiation (n=25*)
Distant metastasis at 3 years		
No	21 (77.8%)	21 (84.0%)
Yes	6 (22.2%)	4 (16.0%)

* With these numbers of analyzable patients, the study now warrants a 13-14% chance of observing a 3-year DM free rate of less than 75% if the true rate is 86% for each arm.

Slide provided by Dr. John Coen
Coen et al. ASCO GU 2018 [J Clin Oncol 36: suppl, abstr 308].

RTOG 0712: Acute toxicity

Distribution of RTOG 0712 Patients by Highest Grade Adverse Event That Occurred during Treatment by Specific Category (GU, GI and Hematologic)

(Any Relationship to Protocol Treatment)

Category	BID Irradiation + 5 Fluorouracil and Cisplatin (n=33)					QD Irradiation + Gemcitabine (n=33)				
	1	2	3	4	5	1	2	3	4	5
Overall Highest Grade	5 (15.2)	9 (27.3)	12 (36.4)	7 (21.2)	0 (0.0)	6 (18.2)	9 (27.3)	16 (48.5)	2 (6.1)	0 (0.0)
Blood/bone marrow	5 (15.2)	8 (24.2)	11 (33.3)	7 (21.2)	0 (0.0)	13 (39.4)	12 (36.4)	6 (18.2)	2 (6.1)	0 (0.0)
Gastrointestinal	12 (36.4)	16 (48.5)	2 (6.1)	0 (0.0)	0 (0.0)	12 (36.4)	17 (51.5)	4 (12.1)	0 (0.0)	0 (0.0)
Renal/genitourinary	15 (45.5)	5 (15.2)	2 (6.1)	0 (0.0)	0 (0.0)	7 (21.2)	10 (30.3)	2 (6.1)	0 (0.0)	0 (0.0)

Adverse events were graded with CTCAE version 3.0.
Overall highest grade is from blood/bone marrow, gastrointestinal, or renal/genitourinary adverse events.

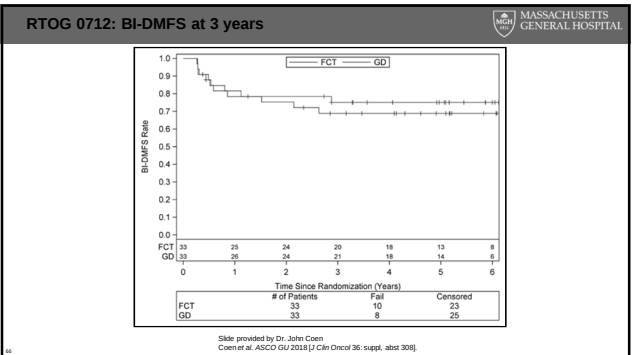
Slide provided by Dr. John Coen
Coen et al. ASCO GU 2018 [J Clin Oncol 36: suppl, abstr 308].

RTOG 0712: Complete response rate

Complete Response Post Induction

	5 Fluorouracil and Cisplatin + BID Irradiation (n=33)	Gemcitabine + QD Irradiation (n=33)
Response of the Primary Tumor Post Induction		
Not a complete response	4 (12.1%)	7 (21.2%)
Complete response	29 (87.9%)	25 (75.8%)
Inevaluable	0 (0.0%)	1 (3.0%)

Slide provided by Dr. John Coen
Coen et al. ASCO GU 2018 [J Clin Oncol 36: suppl, abstr 308].



What is the value of adjuvant chemo?

There is no level 1 evidence for adjuvant chemotherapy post-cystectomy

Adjuvant chemo was associated with disease-specific survival on univariate, but not multivariate, analysis of the MGH/RTOG experience.

Trials: RTOG 9706, 9906, 0233, 0712

Giacalone et al. Eur Urol 2017; 71: 952-960.

What about neoadjuvant chemo?

RTOG 8903: Randomized phase 3
Stage T2 - T4a
(N=123)

```

    graph TD
      TURBT[TURBT] --> Randomization[randomization]
      Randomization --> Chemo[MCV x2  
QD RT  
Cisplatin 100mg/m2 d1, 22]
      Randomization --> NoChemo[No neoadjuvant  
QD RT  
Cisplatin 100mg/m2 d1, 22]
      Chemo --> Result[Result: no difference in OS, DFS,  
mets-free survival w/ neo-adjuvant chemo]
      NoChemo --> Result
  
```

Shipley et al. J Clin Oncol 1998; 16: 3576-3583.

MGH experience with neoadjuvant chemo

1986-2015

What do we do in practice at MGH?

No neoadjuvant chemotherapy for TMT patients

Cystectomy candidate

- Cisplatin-eligible → BID RT + cis/5FU → adjuvant chemo
- Cisplatin-ineligible → QD RT + 5FU/MMC or BIW gemcitabine

Non-cystectomy candidate

- OK for port-a-cath → QD RT + 5FU/MMC
- Doesn't want port-a-cath → QD RT + BIW gemcitabine

**Surveillance and follow-up
Managing recurrences**

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Surveillance after TMT

Cystoscopic surveillance is critical to assure no local recurrence of disease

At 8-12 weeks post-consolidation, cystoscopy and biopsy performed under anesthesia

- Expect persistent eschar/ulceration at tumor resection site
- Debride fibrinous tissue with cold loop and then biopsy viable tissue in bladder wall

Cystoscopy and biopsy repeated at 3 months can convert to office cystoscopy after 2nd negative biopsy

Surveillance schedule: Q3 mo x 1 year → Q4 mo x 1 year → Q6 mo until year 5 → Annually for life

Voided urine cytology

Radiation cystitis

Majority are clinically insignificant
Occasional need for intervention
Of 500 patients, 2 have needed cystectomy for end-stage bladder

4 SCB Test Capture Video

Non-invasive recurrences

Incidence, Clinicopathological Risk Factors, Management and Outcomes of Nonmuscle Invasive Recurrence after Complete Response to Trimodality Therapy for Muscle Invasive Bladder Cancer

Alejandro Sanchez*, Matthew F. Wozniak*, Andrzej Niemierko, Rebecca H. Clayman, Michael Drumm, Dayron Rodriguez, Adam S. Feldman, Douglas M. Dahl, Niall M. Heney, William U. Shipley, Anthony L. Zietman and Jason A. Efstathiou†
THE JOURNAL OF UROLOGY® Vol. 199, 407-415, February 2018

- NMIBC recurrences occurred in 85/342 (25%) complete TMT responders
- CIS univariate, but not multivariate predictor

Log-rank test: P = 0.02

Non-invasive recurrences

Incidence, Clinicopathological Risk Factors, Management and Outcomes of Nonmuscle Invasive Recurrence after Complete Response to Trimodality Therapy for Muscle Invasive Bladder Cancer

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THE JOURNAL OF UROLOGY® Vol. 199, 407-415, February 2018

- 8/85 had immediate cystectomy
- Of those who had TURBT (76):
 - 9 (12%) progressed to MIBC
 - 18 (24%) ultimately had salvage cystectomy

Non-invasive recurrences

Incidence, Clinicopathological Risk Factors, Management and Outcomes of Nonmuscle Invasive Recurrence after Complete Response to Trimodality Therapy for Muscle Invasive Bladder Cancer

Alejandro Sanchez*, Matthew F. Wozniak*, Andrzej Niemierko, Rebecca H. Clayman, Michael Drumm, Dayron Rodriguez, Adam S. Feldman, Douglas M. Dahl, Niall M. Heney, William U. Shipley, Anthony L. Zietman and Jason A. Efstathiou†
THE JOURNAL OF UROLOGY® Vol. 199, 407-415, February 2018

- Those with NMIBC recurrences have worse BSS, but similar OS
- 39 patients had BCG post-TURBT
 - 74% completed BCG induction
 - 36% received maintenance BCG
 - 49% reported BCG toxicity
- At 3 years:
 - Recurrence-free survival 59%
 - Progression-free survival 63%

Non-invasive recurrences – Take home

Patients with adverse features should be offered immediate salvage cystectomy:

- T1 disease
- Tumor > 3cm
- CIS
- Lymphovascular invasion

MIBC recurrences → Salvage cystectomy +/- perioperative chemotherapy

Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience

Nicholas J. Giacalone*, William U. Shipley*, Rebecca H. Clayman*, Andrzej Niemierko*, Michael Drumm*, Niall M. Heney*, Marc D. Michaelson*, Richard J. Lee*, Philip J. Saylor*, Matthew F. Wozniak*, Adam S. Feldman*, Douglas M. Dahl*, Anthony L. Zietman*, Jason A. Efstathiou**
EUROPEAN UROLOGY 71 (2017) 952-960

- The overall need for salvage cystectomy was 29% at 5 years and 31% at 10 years
- 13.5% of the overall cohort had salvage cystectomy for recurrent disease found on surveillance
- 5 and 10 year survival after salvage cystectomy for recurrent disease: 64% and 55%

Salvage Cystectomy rates: Other series

Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic

Girish S. Kulkarni, Thomas Hermann, Yindang Wei, Binod Bhandi, Raj Sekaranarayanan, Paul Athanasopoulos, Peter J. Bottom, Cynthia Kok, Zhenyi Li, Javad J. Zorlioni, Soheil S. Sridhar, Thodoros H. van der Werf, Peter Chung, Robert G. Brinson, Michael Milneric, Padraig Wierle, Neil F. Flehner, Michael A.S. Jewett, Shaheena Baskin, and Alexandre R. Zlotta

J Clin Oncol 35:2299-2306.

Updated results of bladder-sparing trimodality approach for invasive bladder cancer

Almudena Zapatero, M.D., Ph.D., Carmen Martín de Vidales, M.D., Ph.D., Ramón Arellano, M.D., Gloria Bocardo, M.D., Mar Pérez, M.D., Patricia Rios, M.D.

Urologic Oncology: Seminars and Original Investigations 28 (2019) 368–374

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

Nicholas D. James, M.B., B.S., Ph.D., Syed A. Hussain, M.B., B.S., M.D., Emma Hall, Ph.D., Peter Jenkins, M.B., B.S., Ph.D., Jean Tremblay, M.Sc., Christine Rawlings, M.Sc., Malcolm Crundwell, M.D., B.Chir., Bruce Sizer, M.B., B.S., Thiagarajan Srinivasan, M.B., B.S., Carey Hendron, M.Sc., Rebecca Lewis, B.Sc., Rachel Waters, M.Sc., and Robert A. Huddart, M.B., B.S., Ph.D., for the BC2001 Investigators

N Engl J Med 366:1477-88.

• Median follow-up 4.51 years

• Need for salvage cystectomy: 10.7%

• Mean follow-up 4.5 years

• Need for salvage cystectomy: 8%

• Mean follow-up 5.8 years

• Need for salvage cystectomy: 11.4%

Salvage Cystectomy – Oncologic outcomes

RTOG Pooled Analysis – Disease Specific Survival

Years from Randomization	Patients at risk
0	100
1	85
2	65
3	50
4	45
5	41
6	34
7	30
8	17
9	13
10	8

Morbidity of salvage radical cystectomy

Complications and Long-Term Results of Salvage Cystectomy After Failed Bladder Sparing Therapy for Muscle Invasive Bladder Cancer

Jairam R. Eswara*,† Jason A. Efsthathiou,† Niall M. Heney,† Jonathan Paly,† Donald S. Kaufman,† W. Scott McDougall,† Francis McGovern† and William U. Shipley†

THE JOURNAL OF UROLOGY® Vol. 187, 483-488, February 2012

Clavien Grade

Grade	<90 days	MSKCC
1	58 45%	26%
2	48 38%	62%
3	18 14%	11%
4	2 2%	0%
5	2 2%	2%

• All patients had cutaneous diversions

• 3/91 (3%) had an intraop rectal injury → 2 repaired, 1 colostomy

• At 90 days: 69% any complication; 16% major complication

• Cardiovascular/hematologic complications (PE, MI, DVT, transfusion) more common in immediate cystectomy → ? Recent chemotherapy

• Tissue healing complications (wound, anastomoses, stoma) more common in delayed cystectomy → ? Higher radiation dose (64.7 vs 39.9 Gy)

Compared to MSKCC series:

• Overall complication rate: 69 vs. 64%

• Major complication rate: 16% vs. 13%

• Mortality 2.2% vs. 2.7%

Salvage Cystectomy - Summary

• salvage cystectomy after radiation has slightly higher complication rate

• therapy is usually followed by ileal conduit or continent cutaneous reservoir

• neobladder not impossible, but accompanied by higher risk strictures and incontinence

Quality of life

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Toxicity is acceptable and Quality of life after bladder preservation is good

TMT Clinical Trials

- RTOG trials: 157 patients treated with TMT who survived 2-13 years (median follow-up 5.2 years)

Late Pelvic Toxicity	
Grade 1	22%
Grade 2	10%
Grade 3	7.6% (5.7% GU, 1.9% GI)
Grade 4	0%
Grade 5	0%

- BC2001: 360 patients treated with radiation vs. TMT
 - Grade 3-4 late toxicity: GU 3.3%; GI 0.8%

Elfstathiou JA, et al. JCO 2009
James ND, et al. NEJM 2012

MGH Urodynamics and QOL Study

221 patients treated with TMT on protocols
1986-2000, median follow-up 6.3 years

- **78% have compliant bladders** with normal capacity and flow parameters
 - **85% have no or occasional urgency**
- 25% have occasional to moderate bowel control symptoms
- 50% of men have normal erectile function

Zietman AL, et al. J Urol 2003

QoL due to urinary symptoms after TMT

If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?

delighted	pleased	mostly satisfied	mixed – about equally satisfied and dissatisfied	mostly dissatisfied	unhappy	terrible
18.5%	51.7%	17.2%	9.1%	0.8%	2%	0.7%

Weiss et al JCO 2005

Comparing Quality of Life after Surgery vs. Trimodality Therapy

Little data comparing quality of life (QOL) after radical cystectomy (RC) vs. TMT¹

- Randomized trial comparing RC to TMT (SPARE) closed early due to poor accrual²
- Both treatments have long-term effects on overall QOL, urinary, bowel, and sexual function, and self-image³

1. Lagrange JL, et al. UROBP 2011
2. Huddart RA, et al. SJU 2010
3. Porter MP, et al. J Urol 2005

Cystectomy vs. Radiation

Cross-sectional study from Karolinska Institute, Sweden
251 patients treated with cystectomy (incontinent and continent diversions)
58 patients treated with radiation
310 “control” individuals from general population

Urinary function

- After radiation: 74% had no or little urinary symptom distress

Bowel function

- After radiation: 32% had moderate or much bowel distress
- After cystectomy: 24%
- Control group: 9%

Sexual function

- After radiation: 38% had intercourse in last month
- After cystectomy: 13%

Henningsohn L, et al. Radiother Oncol 2002

Review of TMT QOL Studies

Systematic review of 6 QOL studies after TMT
(2 prospective, 4 retrospective)

TMT associated with:

- **Good general QOL** compared to cystectomy
- **Satisfactory urinary function**
- Likely more bowel symptoms than cystectomy
- **Satisfactory sexual function**

Included studies were limited by sample size, variable follow-up, and non-validated instruments

Feuerstein MA, et al. Curr Urol Rep 2015

MGH/UNC: Long-Term QOL 

Cross-sectional study of 173 patients diagnosed in 1990-2011, disease-free for 22 years

Treated at high-volume, academic medical centers with modern techniques

Median follow-up: 5.6 years

- 63% patients received cystectomy (n=109)
- 82% ileal conduit and 18% neobladder diversions
- 37% received TMT (n=64)
- 9% required salvage cystectomy (n=6)

Six validated QOL questionnaires, scored out of 100

Mak et al. IJROBP 2016

Validated Instruments 

General HRQOL:

- 1) EuroQOL EQ-5D: 3L and visual analog scale
- 2) European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30)

Symptom-specific HRQOL:

- 3) EORTC MIBC module (QLQ-BLM30)
- 4) Expanded Prostate Cancer Index Composite - Bowel Assessment (EPIC)

Perception and Impact of Cancer:

- 5) Cancer and Treatment Perception Scale
- 6) Impact of Cancer – Version 2 (IOCv2)

Each instrument scaled to 0-100 score

Mak et al. IJROBP 2016

MGH/UNC: Long Term Quality of life 

- Both cystectomy and TMT associated with good long-term QOL outcomes
- In MGH/UNC study, using 6 validated QOL instruments compared to RC, TMT associated with:
 - Modestly higher general QOL (by 7-10 points)
 - Similar urinary scores
 - Modestly higher bowel function (by 3-7 points)
 - **Markedly better sexual QOL** (by 9-32 points)
 - **Better informed decision-making** (by 14 points)
 - **Less concerns about appearance** (by 14 points)
 - **Less life interference from cancer or cancer treatment** (by 9 points)

Mak et al. IJROBP 2016

Does TMT offer better QOL than Cystectomy? 



Sexual function Urinary function Bowel function?

Adjustment to appearance and life interference General QOL?

Informed decision-making Bowel function?

General QOL?

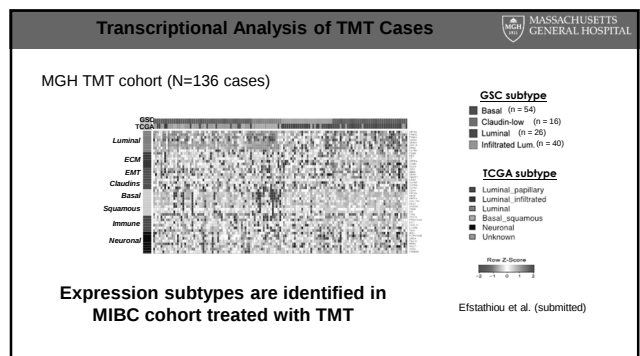
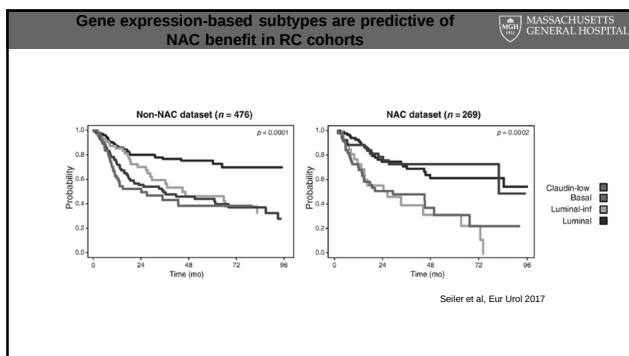
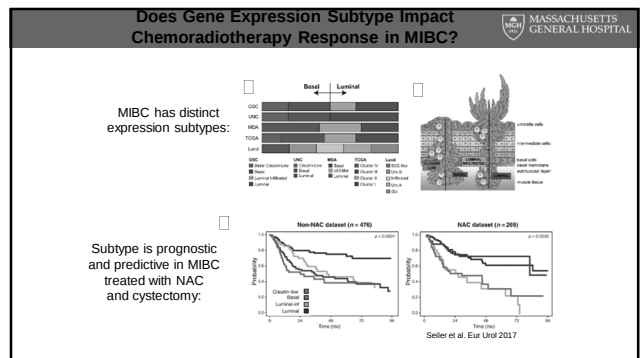
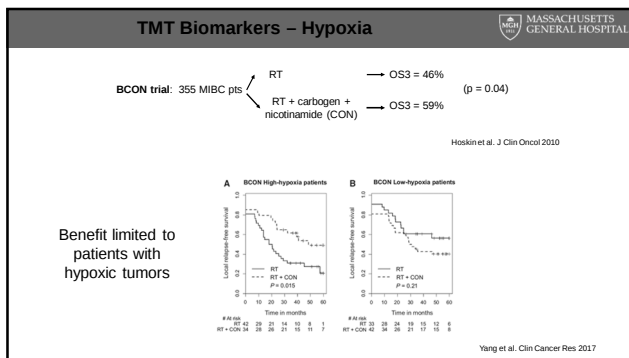
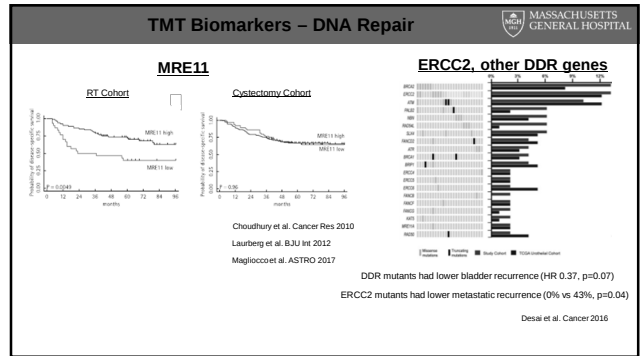
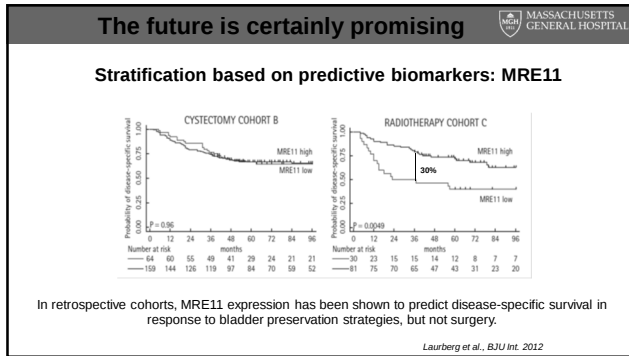
Biomarkers and future directions

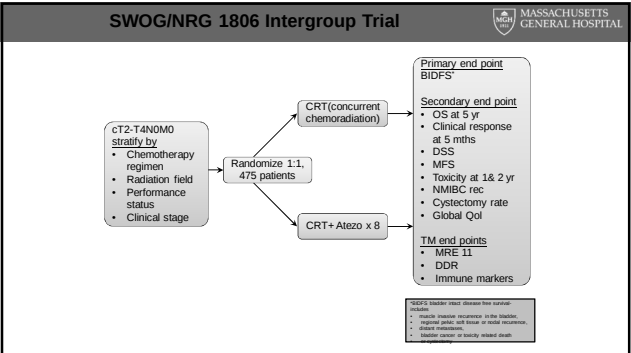
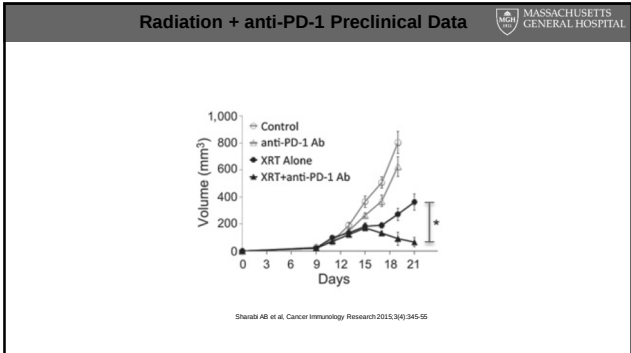
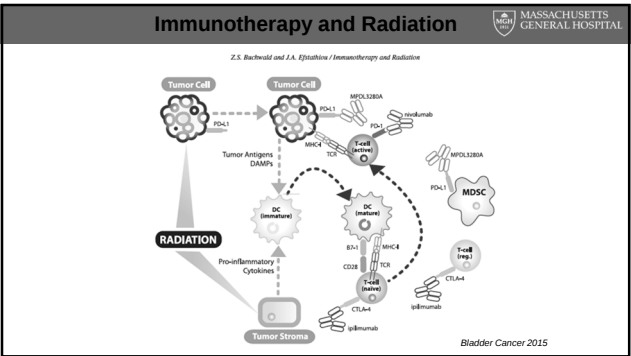
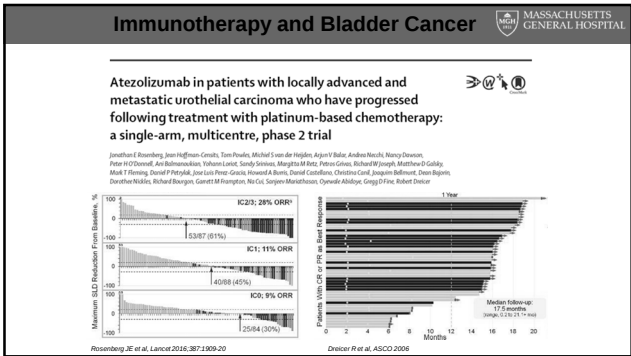
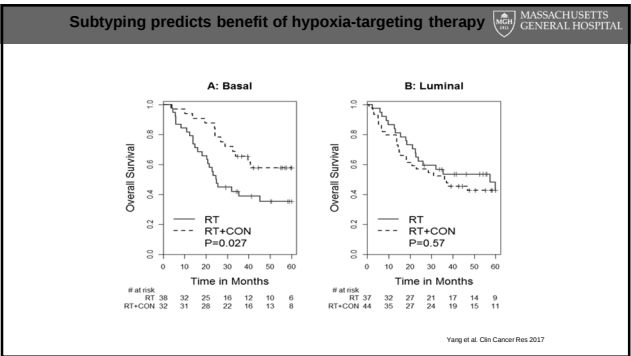
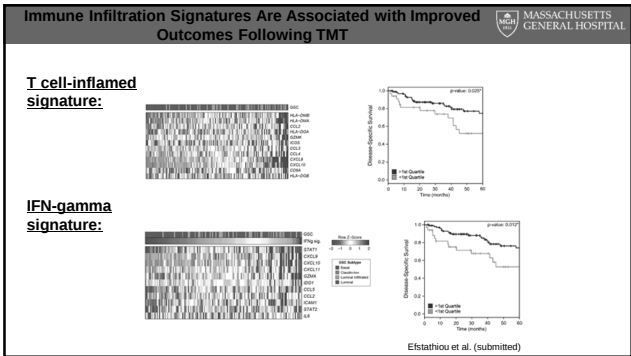
 **MASSACHUSETTS GENERAL HOSPITAL**
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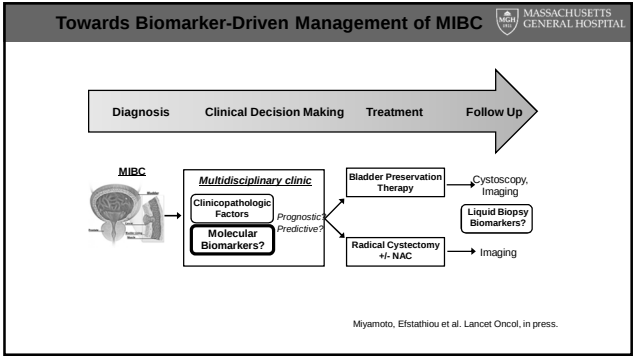
Clinical-Pathologic Factors Impact TMT Decisions 

- Tumor size, T stage
- CIS
- Hydronephrosis (prognostic vs predictive?)
- Renal function
- Bladder function

Can genomic factors inform bladder-sparing therapy?







Closing Thoughts

- Many MIBC pts are not getting curative treatment
➢ *undertreated and underserved population*
- TMT achieves CR and preserves the native bladder nowadays in up to 85% of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series in *selected* patients
- Long-term HRQOL of TMT is good
- These results support such therapy as an acceptable alternative to cystectomy for selected patients (supported by EAU, NCCN, NICE guidelines)
- Need to validate predictive biomarkers for personalized treatment selection and optimize concurrent and adjuvant therapies
- Need continued multidisciplinary engagement and allow patient directed informed decision making

Bladder preservation requires multidisciplinary teamwork

MASSACHUSETTS GENERAL HOSPITAL Rebecca H. Clayman Douglas M. Dahl Michael Drumm Jason A. Elfstathiou Alex Edelstein Adam S. Feldman Nicholas Giacalone Pablo Gomery Mukesh Harisinghani Noel M. Henry Donald S. Kaufman Richard J. Lee Kimberley S. Mak Frank J. McGovern Deor M. Michaelson David Miyamoto Andrag Nemierka Christina Olsen Aria Oumi Michael L. Blute Jon J. Paly William U. Shipley Daphna Y. Spiegel Matthew F. Wozniak Chin-Lue Wu Robin H. Young Anthony L. Zisman	NRG ONCOLOGY Ronald Chen John Coen Wally Curran Felix Feng Ted Harrison Anthony Magliocco Stephanie Pugh Howard Sandler Jeff Simko Kathryn Winter Simon Oncology Group Sameer Jhavar Seth Lerner David McConkey Joshua Meeks Parminder Singh Greg Swanson Cathy Tangen BEUTLER-ACRIN Pietros Krivas Noah Hahn BRISQ Brian Costello Bishoy Faltas Jonathan Rosenberg	DANA-FARBER CANCER CENTER Kent Moun UNMC Matthew Kitzewsky Matthew Nielsen Angie Smith PROTON PROTON Pavel Blaca UNIVERSITAT ROLAND SELLER GenomeDX Christine Buerki Vivek Choudhury Elai Davicioni Marguerite de Plessis Nicholas Erho Ewan Gibb Tyler Kolosiek Seagie Liu Qing Wang Patients/ Patient Advocates BCAN Rick Bangs James Rooney
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Systemic Therapy for Metastatic Prostate Cancer

Comprehensive Review of Urology series

Richard J. Lee, M.D., Ph.D.

Assistant Professor of Medicine, Harvard Medical School
Assistant Physician, Mass General Cancer Center
31 August 2018


**MASSACHUSETTS
GENERAL HOSPITAL
CANCER CENTER**

Relevant disclosures

Research funding: Janssen LLC

Advisory board: Janssen LLC


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Learning objectives

1. Discuss data regarding the use of systemic therapy in patients with recurrent/metastatic prostate cancer
2. Describe possible sequences of therapies for patients with metastatic prostate cancer


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Why prostate cancer?

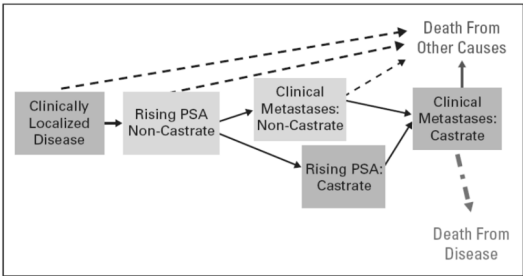
Estimated New Cases
Estimated Deaths

Cancer Site	New Cases	Deaths	% of Males
Lung & bronchus	83,550	26%	
Prostate	29,430	9%	
Colon & rectum	27,390	8%	
Pancreas	23,020	7%	
Liver & intrahepatic bile duct	20,540	6%	
Leukemia	14,270	4%	
Esophagus	12,850	4%	
Urinary bladder	12,520	4%	
Non-Hodgkin lymphoma	11,510	4%	
Kidney & renal pelvis	10,010	3%	
All Sites	323,630	100%	


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Siegel et al. *CA Cancer J Clin* 2018; **68**: 7-30.

Defining the disease: advanced prostate cancer has multiple disease states



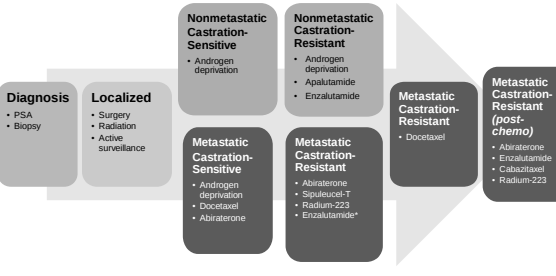
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graph LR
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    B --> C[Clinical Metastases: Non-Castrate]
    B --> D[Rising PSA: Castrate]
    C --> E[Clinical Metastases: Castrate]
    D --> E
    E --> F[Death From Other Causes]
    E --> G[Death From Disease]
    
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Scher et al (2008) *J Clin Oncol* **26**: 1148-1159.

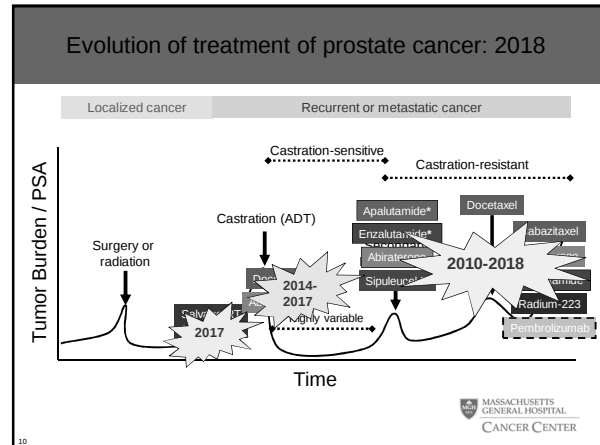
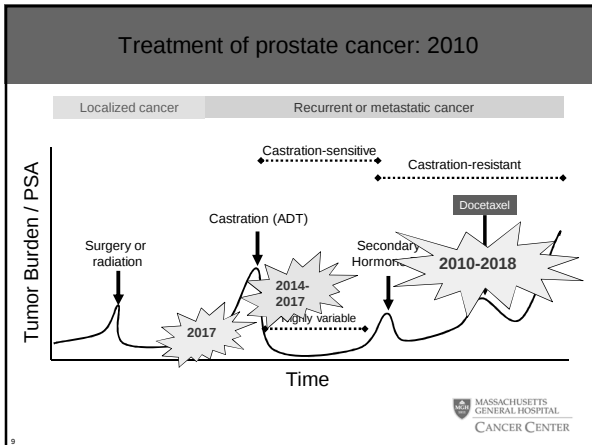
Defining the disease: advanced prostate cancer has multiple disease states



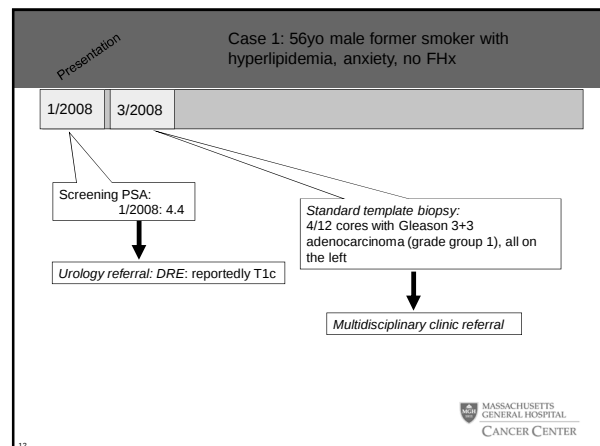
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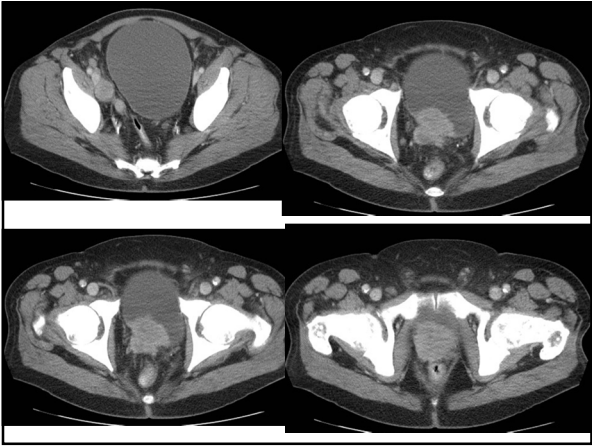
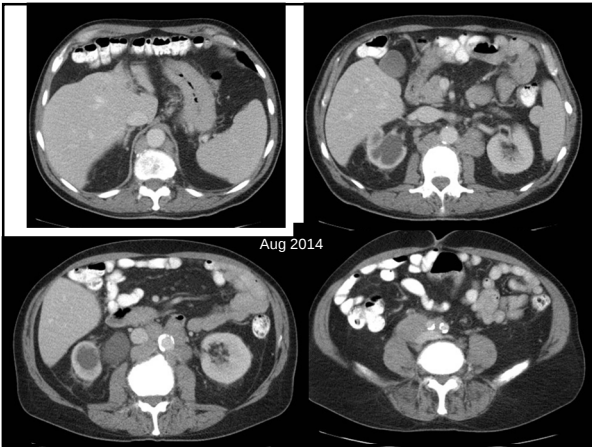
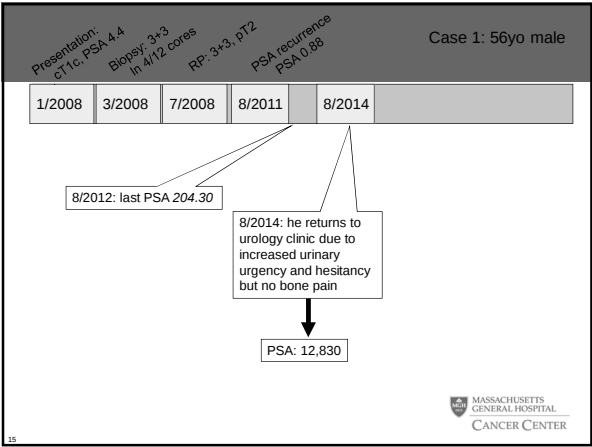
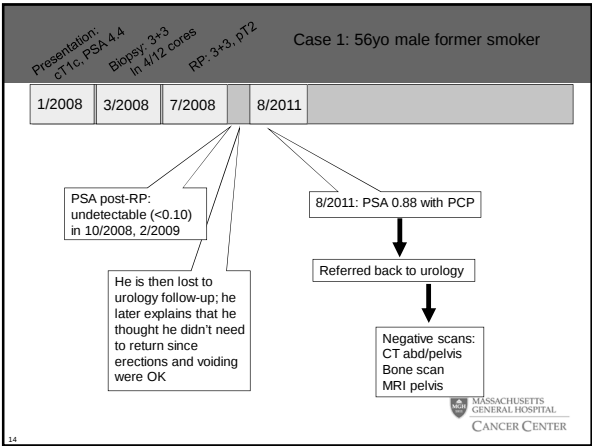
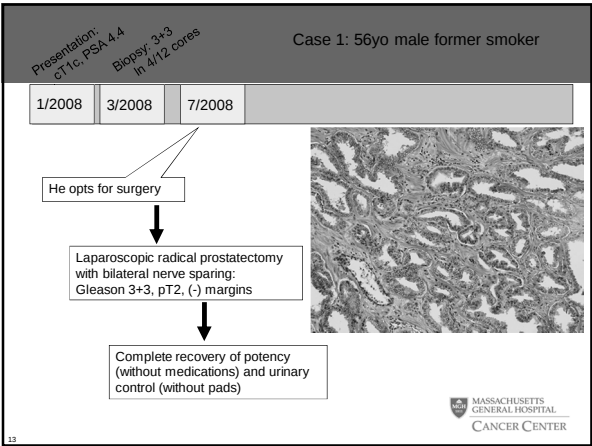
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• PSA  
• Biopsy] --> B[Localized  
• Surgery  
• Radiation  
• Active surveillance]
    B --> C[Nonmetastatic Castration-Sensitive  
• Androgen deprivation]
    B --> D[Nonmetastatic Castration-Resistant  
• Androgen deprivation  
• Apalutamide  
• Enzalutamide]
    C --> E[Metastatic Castration-Sensitive  
• Androgen deprivation  
• Docetaxel  
• Abiraterone]
    D --> F[Metastatic Castration-Resistant  
• Abiraterone  
• Sipuleucel-T  
• Radium-223  
• Enzalutamide*]
    E --> G[Metastatic Castration-Resistant  
• Docetaxel]
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• Cabazitaxel  
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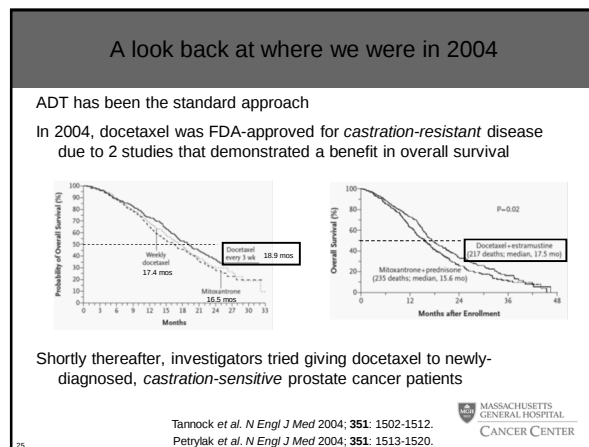
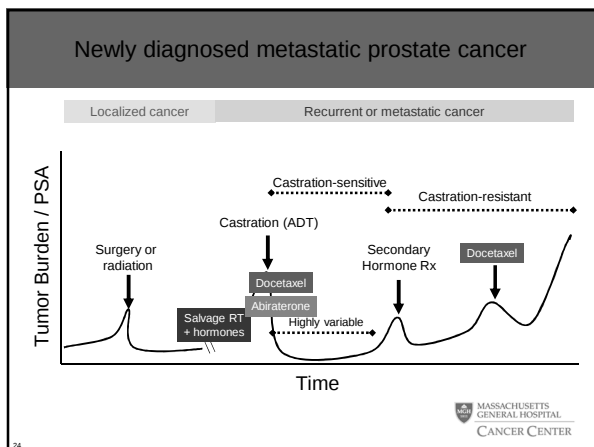

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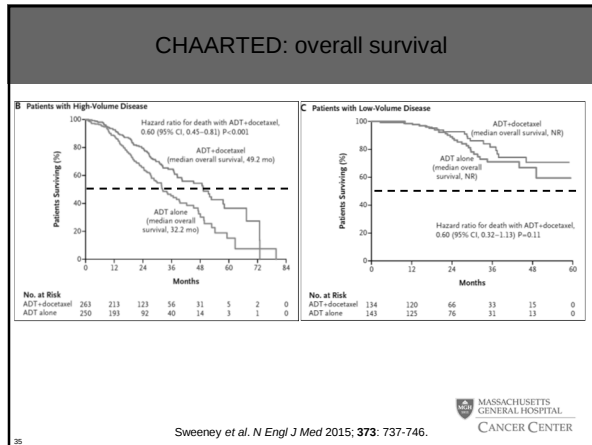
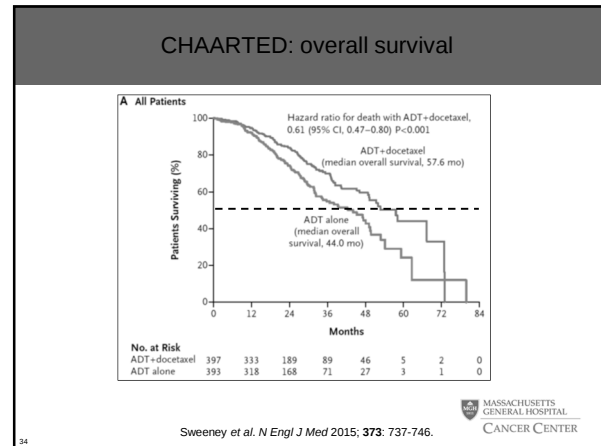
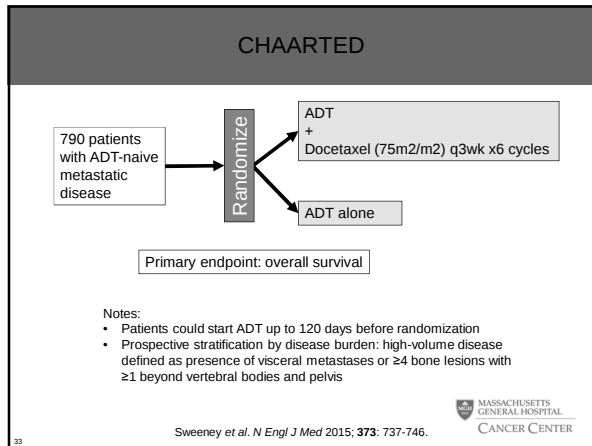
FDA-approved drugs for CRPC	
Improved Overall Survival • 4/29/10: sipuleucel-T • 6/17/10: cabazitaxel (post-docetaxel) • 4/28/11: abiraterone (post-docetaxel) • 8/31/12: enzalutamide (post-docetaxel) • 12/10/12: abiraterone (pre-docetaxel) • 5/15/13: radium-223 dichloride • 9/10/14: enzalutamide (pre-docetaxel)	Improved Metastasis-Free Survival (M0) • 2/14/18: apalutamide • 7/13/18: enzalutamide
MSI-H / dMMR cases • 5/23/17: pembrolizumab	
Supportive Care • Zoledronic acid • Denosumab	







591



Clinical interpretation – CHAARTED

6 cycles of docetaxel is an appropriate option for men with high-burden metastatic prostate cancer starting ADT

Whether docetaxel is appropriate for low-burden disease will require longer follow-up, but is a discussion for patients and their treating clinicians

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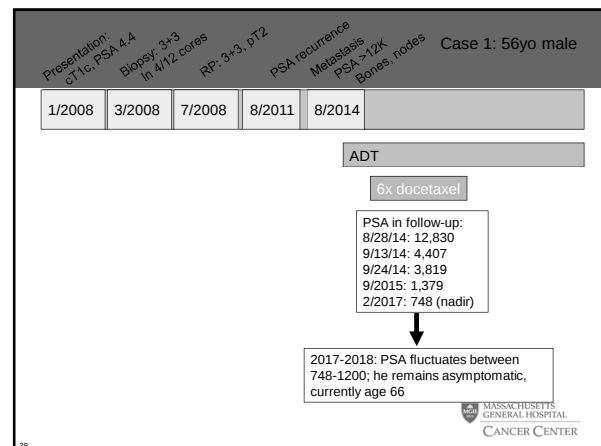
Compare the OS benefit with FDA-approved drugs for mCRPC!

Improved Overall Survival

- 5/19/04: docetaxel
- 4/29/10: sipuleucel-T
- 6/17/10: cabazitaxel (post-docetaxel)
- 4/28/11: abiraterone (post-docetaxel)
- 8/31/12: enzalutamide (post-docetaxel)
- 12/10/12: abiraterone (pre-docetaxel)
- 5/15/13: radium-223 dichloride
- 9/10/14: enzalutamide (pre-docetaxel)

magnitude of survival benefit: 2-5 months

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What about earlier use of abiraterone in metastatic castration-naïve prostate cancer?

Background

- Abiraterone inhibits cytochrome P450c17 and thus inhibits androgen biosynthesis, including extragonadal synthesis (adrenal, intratumoral)
- Abiraterone increased overall survival in the metastatic castration-resistant prostate cancer (mCRPC) setting
- Abiraterone has been shown to decrease tumor burden in high-risk localized disease as neoadjuvant therapy
- Abiraterone acetate is orally bioavailable

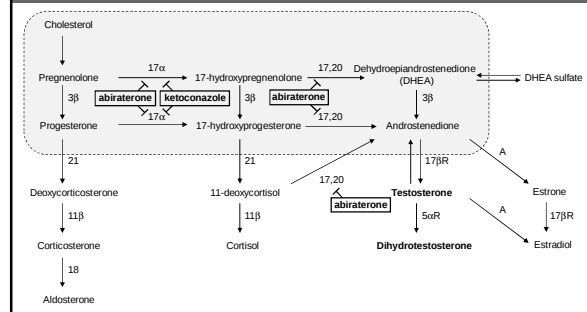
Question

- Is there a benefit to inhibiting extragonadal androgens *before* the development of castration resistance?



40

Steroidogenesis pathways



41

2017: LATITUDE and STAMPEDE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Ozguroglu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

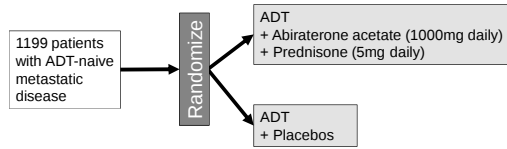
N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillissen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKenna, N. McPhee, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srilani, C. Thomas, J. Wagstaff, J. Wylie, A. Zarak, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

James et al. *N Engl J Med* 2017; **377**: 338-351.
Fizazi et al. *N Engl J Med* 2017; **377**: 352-360.



43

LATITUDE



Primary endpoints: overall survival, radiographic progression-free survival

Notes:

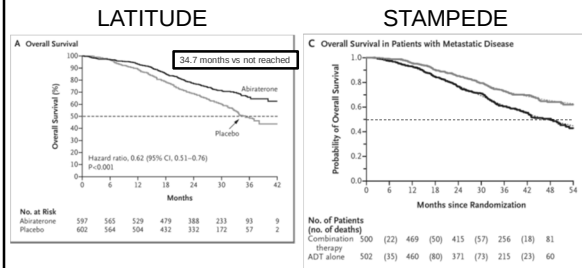
- Patients could start ADT up to 3 months before randomization
- Patients required to have 2 of 3: Gleason score ≥ 8 , at least 3 bone lesions, presence of visceral metastasis
- No stratification by disease burden

Fizazi et al. *N Engl J Med* 2017; **377**: 352-360.



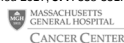
44

Abiraterone studies: primary endpoint: Overall Survival



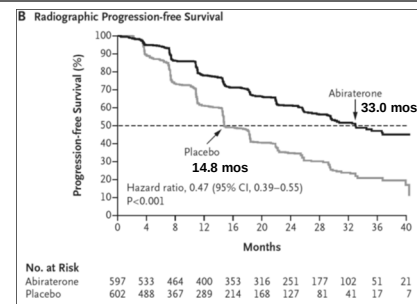
Fizazi et al. *N Engl J Med* 2017; **377**: 352-360.

James et al. *N Engl J Med* 2017; **377**: 338-351.



45

LATITUDE: rPFS

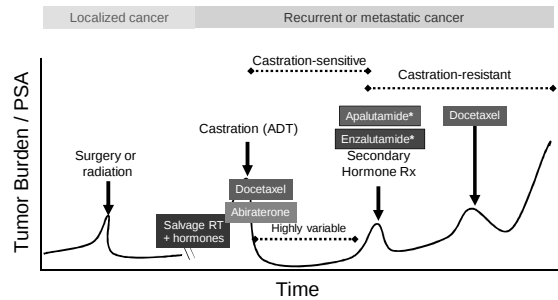


Fizazi et al. *N Engl J Med* 2017; **377**: 352-360.



47

What about further progression? M0 vs M1 CRPC



48

2018: SPARTAN and PROSPER

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Fred Saad, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Stéphane Oudard, M.D., Ph.D., Boris A. Hadaschik, M.D., Julie N. Graff, M.D., David Olmos, M.D., Ph.D., Paul N. Mainwaring, M.B., B.S., M.D., Ji Youl Lee, M.D., Hiroji Uemura, M.D., Ph.D., Angela Lopez-Gitiz, M.D., Gérald C. Trudel, Ph.D., Byron M. Espina, B.S., Youyi Shu, Ph.D., Youn C. Park, Ph.D., Wayne R. Rackoff, M.D., Margaret K. Yu, M.D., and Eric J. Small, M.D., for the SPARTAN Investigators*

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelski, M.D., Ph.D., De Phung, B.S., Andrew Krivosik, M.D., Ph.D., and Cora N. Sternberg, M.D.

Smith et al. *N Engl J Med* 2018; **378**: 1408-1418.
Hussain et al. *N Engl J Med* 2018; **378**: 2465-2474.

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Castration resistance = Androgen independence?

Mechanisms of resistance to hormone therapy

- Androgen production from non-gonadal sources
 - Adrenal glands
 - Tumor cells themselves
- AR gene mutations (18-50%)
- AR gene amplification (up to 30%)
- Ligand-independent AR activation
 - Growth factor receptors: HER2, EGFR, IL-6, IGF-1R
 - Cytoplasmic tyrosine kinases: SRC1, Ack1

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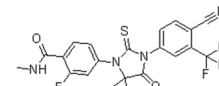
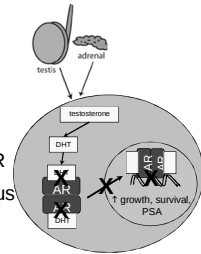
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Enzalutamide (MDV3100, Xtandi)

Oral medication, taken daily

Mechanism of action

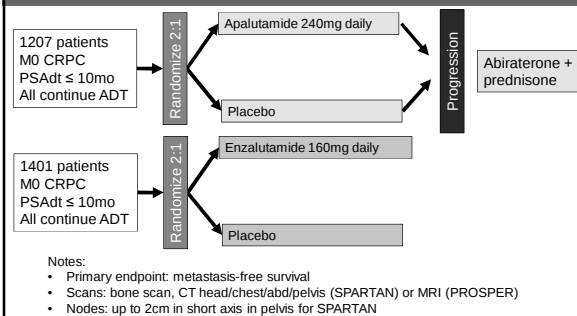
- An anti-androgen
- Competes for androgen binding to AR
- Inhibits AR translocation to the nucleus
- Inhibits binding to DNA



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51

Study designs



- Notes:
- Primary endpoint: metastasis-free survival
 - Scans: bone scan, CT head/chest/abd/pelvis (SPARTAN) or MRI (PROSPER)
 - Nodes: up to 2cm in short axis in pelvis for SPARTAN

Smith et al. *N Engl J Med* 2018; **378**: 1408-1418.
Hussain et al. *N Engl J Med* 2018; **378**: 2465-2474.

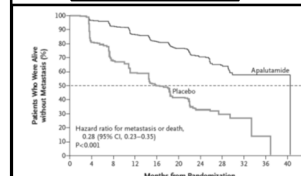
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52

Metastasis-Free Survival

SPARTAN

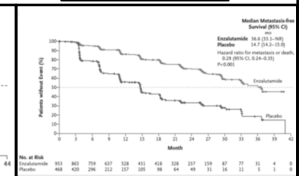
40.5 mo vs 16.2 mo (HR 0.28)



No. at Risk
Apalutamide: 806 713 652 514 398 282 180 96 36 16 3 0 0
Placebo: 402 251 220 153 91 59 34 23 5 1 0 0

PROSPER

36.6 mo vs 14.7 mo (HR 0.29)

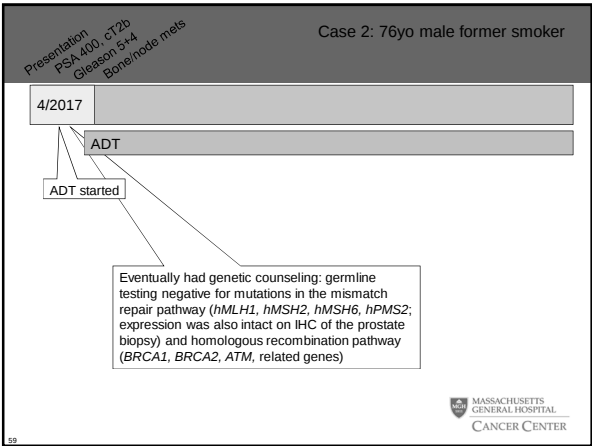
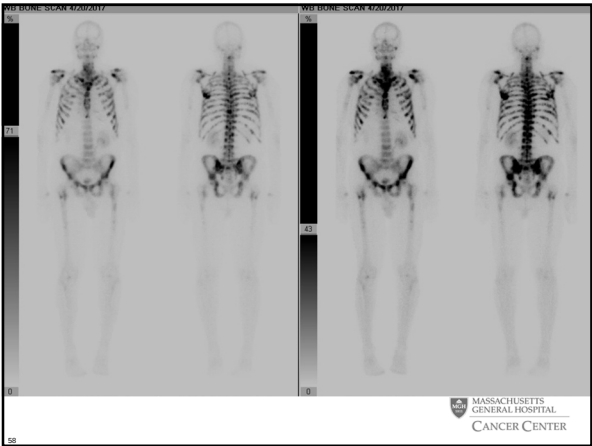
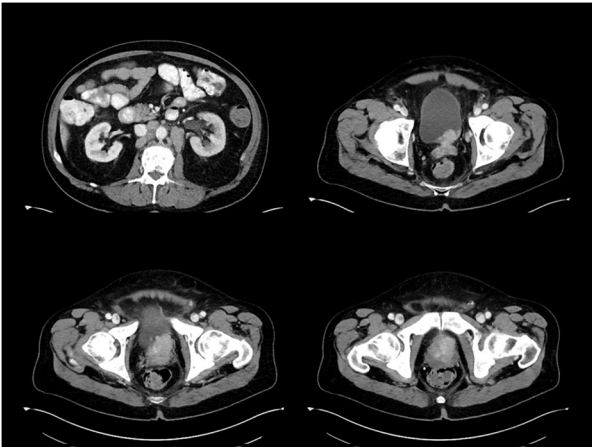
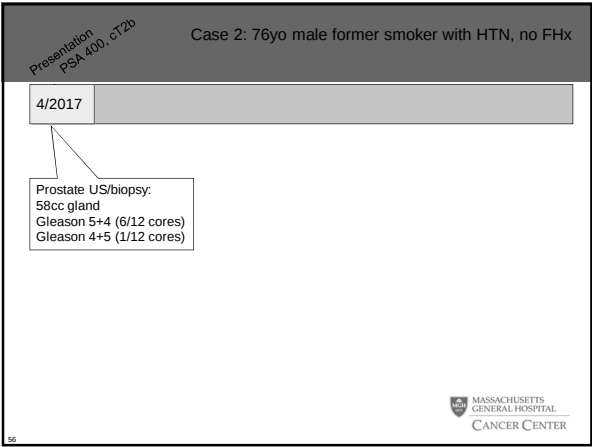
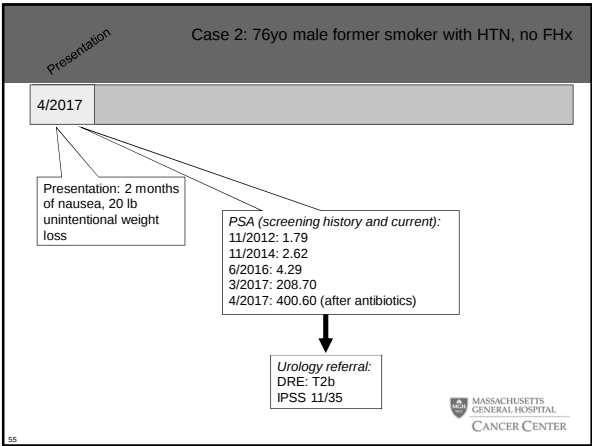
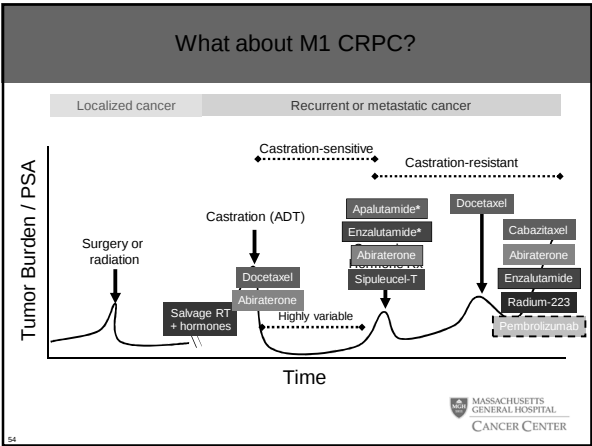


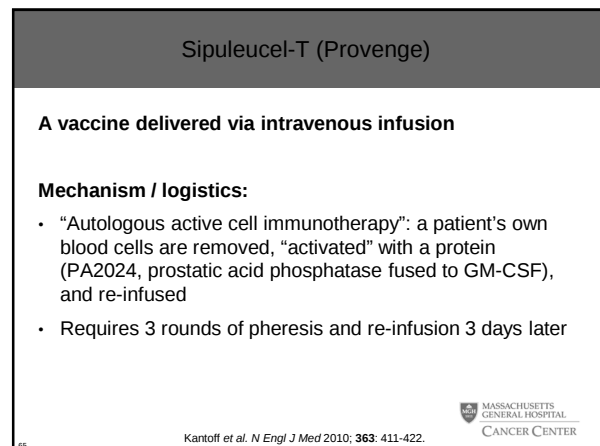
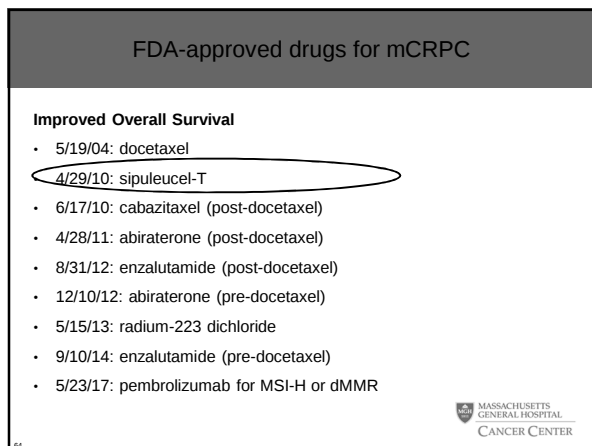
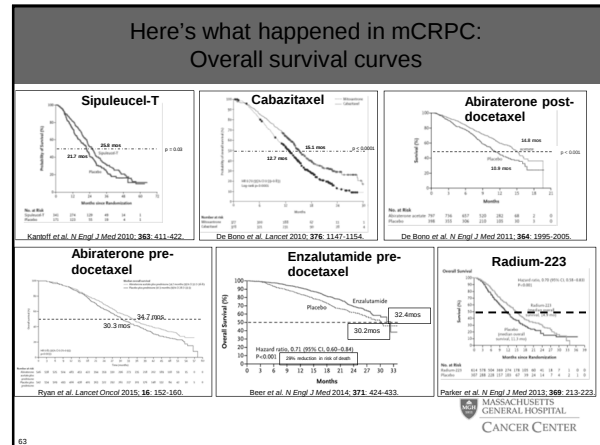
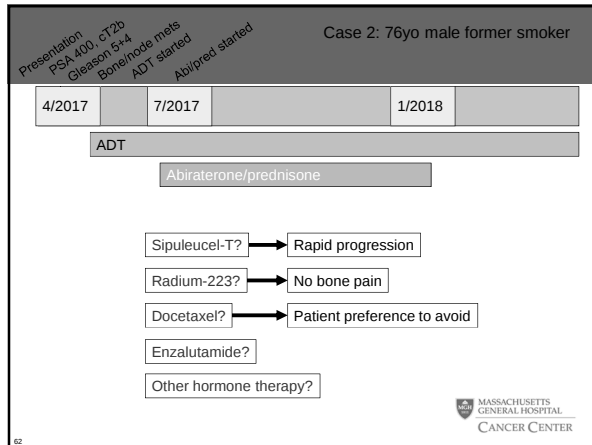
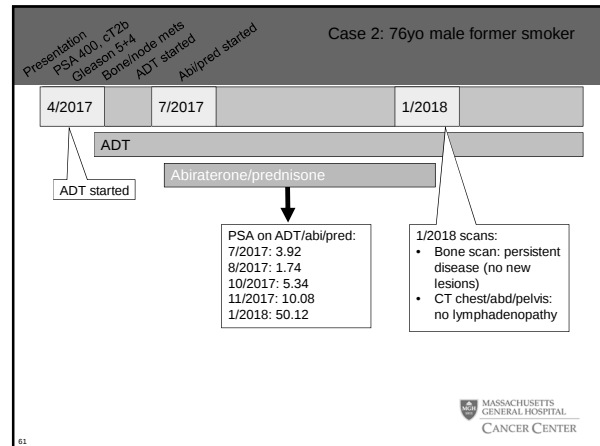
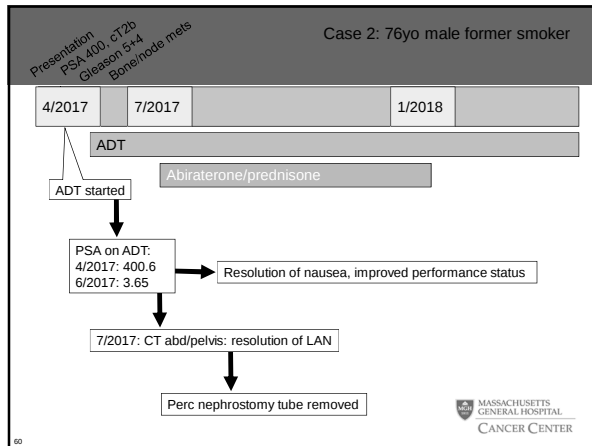
No. at Risk
Enzalutamide: 822 622 522 422 322 222 122 82 42 22 12 4 2
Placebo: 411 211 161 111 61 31 16 8 4 2 1 1 0

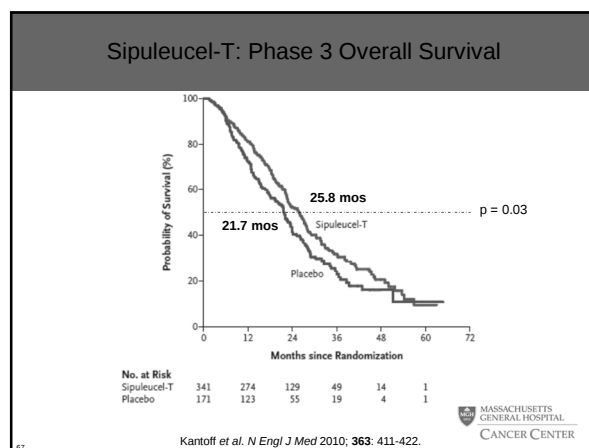
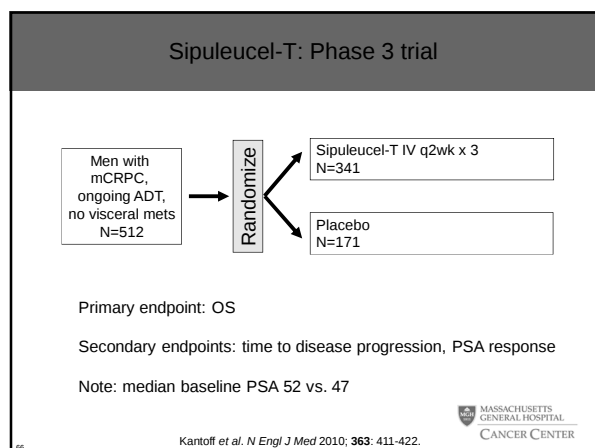
Smith et al. *N Engl J Med* 2018; **378**: 1408-1418.
Hussain et al. *N Engl J Med* 2018; **378**: 2465-2474.

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53







Sipuleucel-T: considerations

How do you know if it's working?

- PSA does not change
- Time to disease progression was not different
- FDA-approved: 4/29/10

How is sipuleucel-T optimally sequenced with other therapies that include immunosuppressants?

Cost: is a 4 month improvement "worth it"?

- \$93,000 for all 3 infusions

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FDA-approved drugs for mCRPC

Improved Overall Survival

- 5/19/04: docetaxel
- 4/29/10: sipuleucel-T
- 6/17/10: cabazitaxel (post-docetaxel)
- 4/28/11: abiraterone (post-docetaxel)
- 8/31/12: enzalutamide (post-docetaxel)
- 12/10/12: abiraterone (pre-docetaxel)
- 5/15/13: radium-223 dichloride
- 9/10/14: enzalutamide (pre-docetaxel)
- 5/23/17: pembrolizumab for MSI-H or dMMR

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Cabazitaxel (Jevtana)

An intravenous chemotherapy like docetaxel

Mechanism: interferes with cell division, but may be less likely to be pumped out of cancer cells than docetaxel

Phase III trial design

- Patients who have progressed on docetaxel therapy

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Cabazitaxel (Jevtana)

An intravenous chemotherapy like docetaxel

Mechanism: interferes with cell division, but may be less likely to be pumped out of cancer cells than docetaxel

Men with mCRPC, ongoing ADT, prior docetaxel ≥ 225mg/m2 N=755

Randomize

Cabazitaxel 25mg/m2 IV q3wk
Prednisone 10mg PO QD N=378

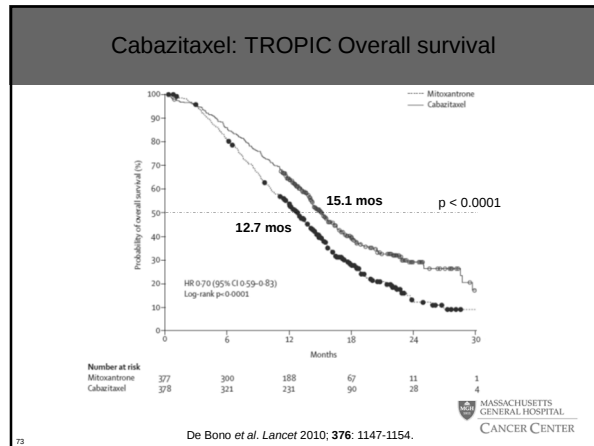
Mitoxantrone 12mg/m2 IV q3wk
Prednisone 10mg PO QD N=377

Primary endpoint: OS

Secondary endpoints: PFS, safety

De Bono et al. *Lancet* 2010; **376**: 1147-1154.

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Cabazitaxel: notes and considerations

The *first* drug to show a survival benefit after docetaxel

FDA-approved: 6/17/10

Adverse events

- More grade 3+ neutropenia (82% vs. 58%) led to more fevers, infections, and deaths (5% vs. 2%)

FDA-approved drugs for mCRPC

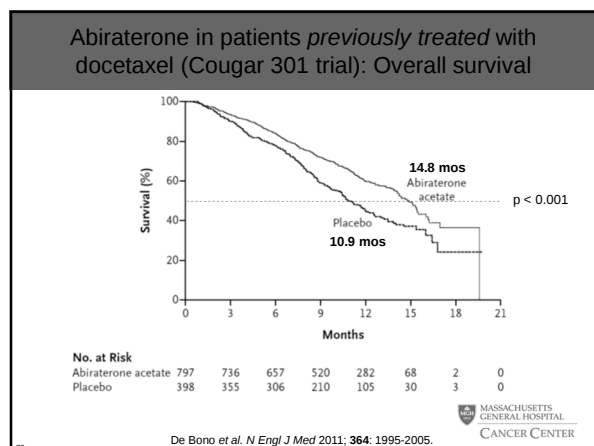
Improved Overall Survival

- 5/19/04: docetaxel
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- 6/17/10: cabazitaxel (post-docetaxel)
- 4/28/11: abiraterone (post-docetaxel)
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- 12/10/12: abiraterone (pre-docetaxel)
- 5/15/13: radium-223 dichloride
- 9/10/14: enzalutamide (pre-docetaxel)
- 5/23/17: pembrolizumab for MSI-H or dMMR

Abiraterone: Cougar 301 phase III trial

Primary endpoint: OS

Secondary endpoints: time to PSA progression, radiographic PFS, PSA response rate



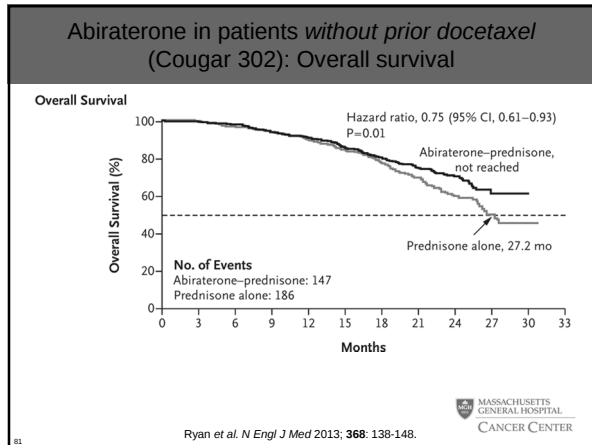
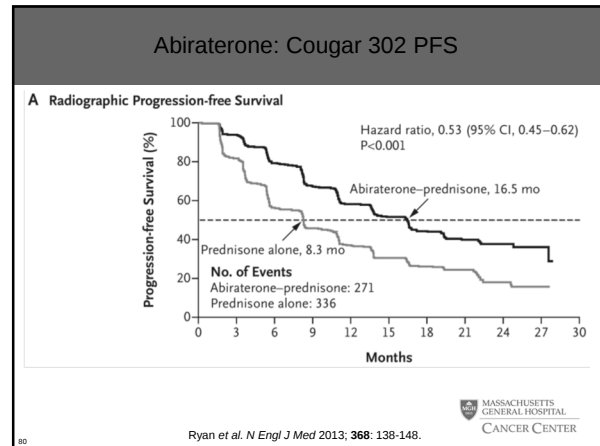
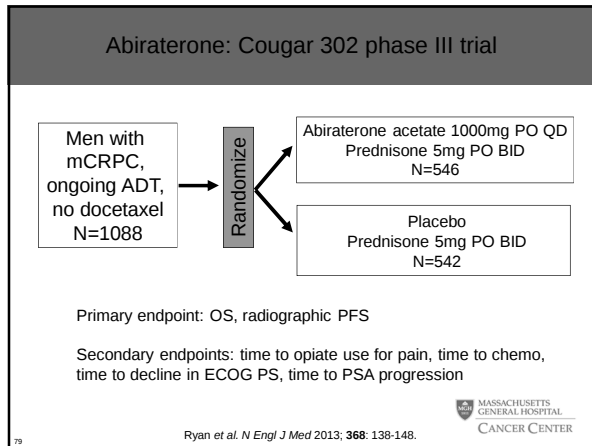
Abiraterone: considerations

The *second* drug (after cabazitaxel) to show a survival benefit after docetaxel

- Longer progression free survival: 5.6 mos vs. 3.6 mos.

Might there be a benefit when given before docetaxel chemotherapy?

- The Cougar 302 study (Phase 3, randomized controlled trial in chemo-naïve patients)...

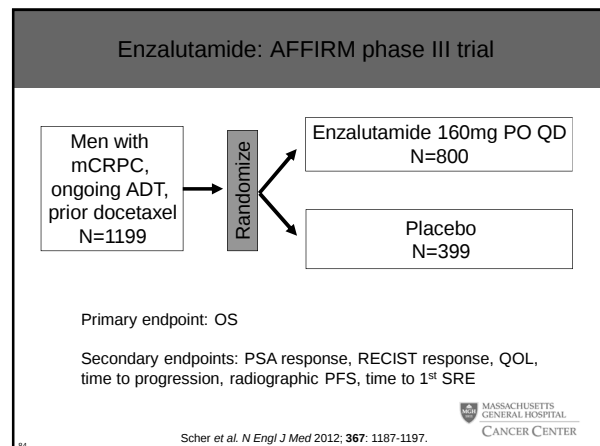
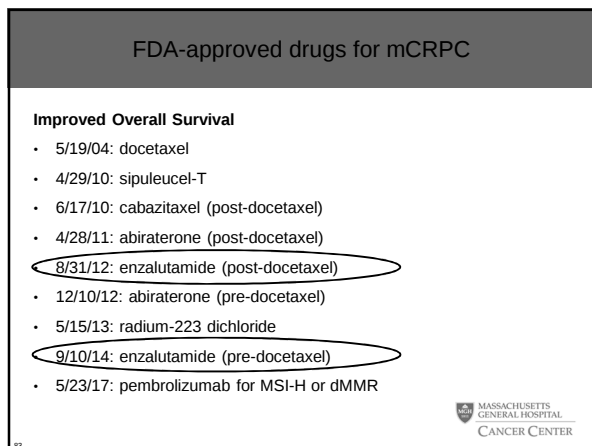


Abiraterone: Cougar 302 secondary endpoints

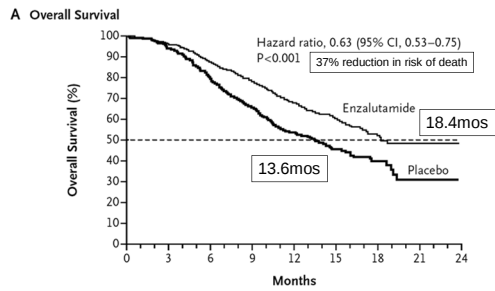
Table 1. Prespecified Secondary and Exploratory Efficacy End Points.*

End Point	Abiraterone-Prednisone (N=546)	Prednisone Alone (N=542)	Value (95% CI)†	P Value
Secondary end points				
Median time to opiate use for cancer-related pain — mo	NR	23.7	0.69 (0.57-0.83)	<0.001
Median time to initiation of cytotoxic chemotherapy — mo	25.2	16.8	0.58 (0.49-0.69)	<0.001
Median time to decline in ECOG performance score by ≥1 point — mo	12.3	10.9	0.82 (0.71-0.94)	0.005
Median time to PSA progression — mo‡	11.1	5.6	0.49 (0.42-0.57)	<0.001
Exploratory end points§				
Median time to increase in pain — mo¶	26.7	18.4	0.82 (0.67-1.00)	0.049
Median time to functional-status decline measured as FACT-P total score — mo	12.7	8.3	0.78 (0.66-0.92)	0.003
Patients with decline of ≥50% in PSA level — %**	62	24	2.59 (2.19-3.05)††	<0.001
Patients with a RECIST response — %‡‡				
Defined objective response	36	16	2.27 (1.59-3.25)††	<0.001
Stable disease	61	69		
Progressive disease	2	15		

82 Ryan et al. *N Engl J Med* 2013; **368**: 138-148.



Enzalutamide: Phase III clinical trial (AFFIRM)



Scher et al. *N Engl J Med* 2012; **367**: 1187-1197.

Enzalutamide: Phase III clinical trial (AFFIRM)

Table 2. Secondary End Points Related to Response and Disease Progression.*

End Point	Enzalutamide (N=800)	Placebo (N=399)	Hazard Ratio (95% CI)	P Value
Confirmed PSA decline†				
Patients with ≥1 postbaseline PSA assessment — no. (%)	731 (91)	330 (83)		
PSA response — no./total no. (%)				
Decline ≥50% from baseline	395/731 (54)	5/330 (2)		<0.001
Decline ≥80% from baseline	181/731 (25)	3/330 (1)		<0.001
Soft-tissue objective response				
Patients with measurable disease — no. (%)	446 (56)	208 (52)		
Complete or partial objective response — no./total no. (%)	129/446 (29)	8/208 (4)		<0.001
FACT-P quality-of-life response‡				
Patients with ≥1 postbaseline assessment — no. (%)	651 (81)	257 (64)		
Quality-of-life response — no./total no. (%)§	281/651 (43)	47/257 (18)		<0.001
Progression indicators				
Time to PSA progression — mo			0.25 (0.20–0.30)	<0.001
Median	8.3	3.0		
95% CI	5.8–8.3	2.9–3.7		
Radiographic progression-free survival — mo			0.40 (0.35–0.47)	<0.001
Median	8.3	2.9		
95% CI	8.2–8.4	2.8–3.4		
Time to first skeletal-related event — mo			0.69 (0.57–0.84)	<0.001
Median	16.7	13.3		
95% CI	14.6–19.1	9.9–16.9		

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Enzalutamide: Phase III clinical trial (AFFIRM)

Table 3. Adverse Events, According to Grade.

Adverse Event	Enzalutamide (N=800)		Placebo (N=399)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
≥1 Adverse event	785 (98)	362 (45)	390 (98)	212 (53)
Any serious adverse event	268 (34)	227 (28)	154 (39)	134 (34)
Discontinuation owing to adverse event	61 (8)	37 (5)	39 (10)	28 (7)
Adverse event leading to death	23 (3)	23 (3)	14 (4)	14 (4)
Frequent adverse events more common with enzalutamide*				
Fatigue	269 (34)	50 (6)	116 (29)	29 (7)
Diarrhea	171 (21)	9 (1)	70 (18)	1 (<1)
Hot flash	162 (20)	0	41 (10)	0
Musculoskeletal pain	109 (14)	8 (1)	40 (10)	1 (<1)
Headache	93 (12)	6 (<1)	22 (6)	0
Clinically significant adverse events				
Cardiac disorder				
Any	49 (6)	7 (1)	30 (8)	8 (2)
Myocardial infarction	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Abnormality on liver-function testing†	8 (1)	3 (<1)	6 (2)	3 (<1)
Seizure	5 (<1)	5 (<1)	0	0

Scher et al. *N Engl J Med* 2012; **367**: 1187-1197.

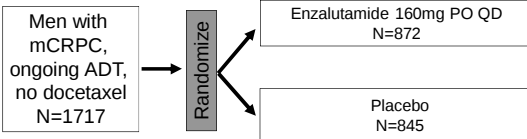
Enzalutamide: considerations

Another option that extends survival after docetaxel

Might there be a benefit when given before docetaxel chemotherapy?

- PREVAIL (Phase 3, randomized controlled trial in chemo-naïve patients)...

Enzalutamide in patients without prior docetaxel (PREVAIL phase III trial)

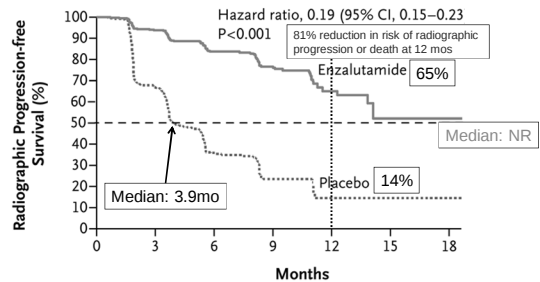


Primary endpoint: OS, radiographic PFS

Secondary endpoints: PSA response, soft tissue response, QOL

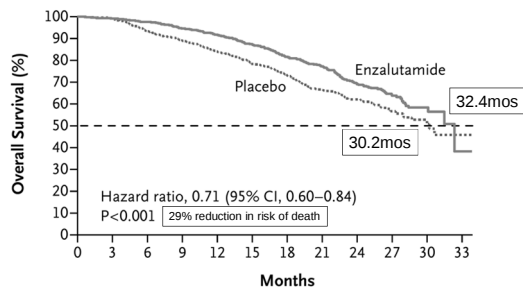
Beer et al. *N Engl J Med* 2014; **371**: 424-433.

Enzalutamide in patients without prior docetaxel (PREVAIL): progression-free survival



Beer et al. *N Engl J Med* 2014; **371**: 424-433.

Enzalutamide in patients *without prior docetaxel* (PREVAIL): Overall survival



Beer et al. *N Engl J Med* 2014; 371: 424-433.

FDA-approved drugs for mCRPC

Improved Overall Survival

- 5/19/04: docetaxel
- 4/29/10: sipuleucel-T
- 6/17/10: cabazitaxel (post-docetaxel)
- 4/28/11: abiraterone (post-docetaxel)
- 8/31/12: enzalutamide (post-docetaxel)
- 12/10/12: abiraterone (pre-docetaxel)
- 5/15/13: radium-223 dichloride
- 9/10/14: enzalutamide (pre-docetaxel)
- 5/23/17: pembrolizumab for MSI-H or dMMR

Radium-223 dichloride (Xofigo)

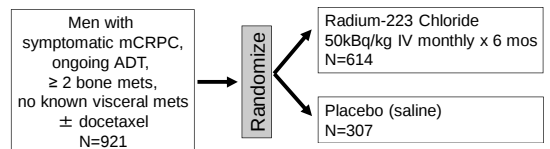
An intravenous radiation treatment

Mechanism

- A radioisotope containing an α -emitting nuclide
- Targets bone metastases with high-energy α radiation of extremely short range that spares bone marrow, limiting toxic effects
- For patients with bone-only or bone-dominant disease

Logistics: monthly infusions x 6 months

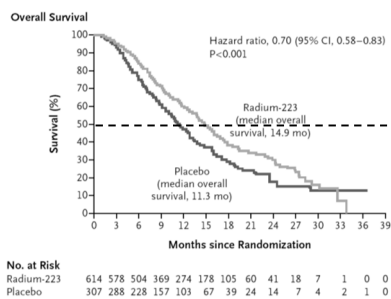
Radium-223: ALSYMPCA phase III trial



Primary endpoint: OS

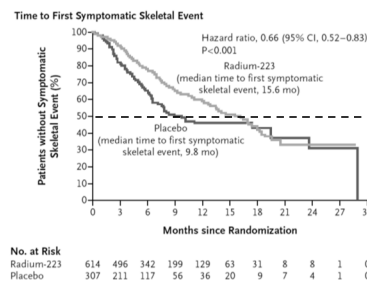
Secondary endpoints: time to first symptomatic skeletal event, various biochemical endpoints

Radium-223: ALSYMPCA trial – Overall Survival



Parker et al. *N Engl J Med* 2013; 369: 213-223.

Radium-223: ALSYMPCA – first symptomatic SRE (skeletal related event)



Parker et al. *N Engl J Med* 2013; 369: 213-223.

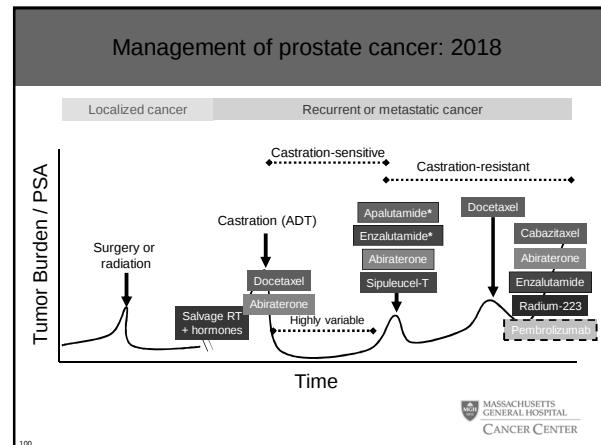
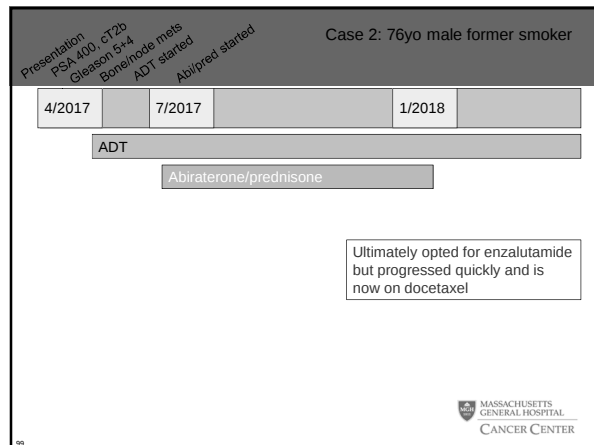
mCRPC and overall survival					
	Agent(s)	N	OS	improvement	P
Docetaxel-Naïve	Mitoxantrone + hydrocortisone	119	12.3mo	0.3mo	0.77
	Hydrocortisone	123	12.6mo		
	Docetaxel/estramustine	338	17.5mo	1.9mo	0.02
	Mitoxantrone	336	15.6mo		
	Docetaxel/prednisone q3wk	335	18.9mo		
	Docetaxel/prednisone q1wk	334	17.4mo	2.4mo	0.009
	Mitoxantrone/prednisone q3wk	337	16.5mo		0.36
	Abiraterone acetate/prednisone	546	34.7mo	4.4mo	0.01
	Placebo/prednisone	542	30.3mo		
	Sipuleucel-T	341	25.8mo	4.1mo	0.03
+/- Docetaxel	Placebo	171	21.7mo		
	Radium-223 chloride	541	14.0mo	2.8mo	0.00046
	Placebo	268	11.2mo		
Docetaxel-pretreated	Cabazitaxel/prednisone	378	15.1mo	2.4mo	<0.0001
	Mitoxantrone/prednisone	377	12.7mo		
	Abiraterone acetate/prednisone	797	14.8mo	3.9mo	<0.001
	Prednisone	398	10.9mo		
	Enzalutamide	800	18.4mo	4.8mo	<0.001
	Placebo	399	13.6mo		

FDA-approved drugs for mCRPC

Improved Overall Survival

- 5/19/04: docetaxel
- 4/29/10: sipuleucel-T
- 6/17/10: cabazitaxel (post-docetaxel)
- 4/28/11: abiraterone (post-docetaxel)
- 8/31/12: enzalutamide (post-docetaxel)
- 12/10/12: abiraterone (pre-docetaxel)
- 5/15/13: radium-223 dichloride
- 9/10/14: enzalutamide (pre-docetaxel)
- 5/23/17: pembrolizumab for MSI-H or dMMR

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Despite all the progress, there's work to be done

Outstanding questions

- With so many drugs, what is the optimal sequence?
- What do we know about resistance to therapies?
- Can we identify cellular changes (genetic or other) that may explain more aggressive cancer behavior in black patients?
- What is the role for immunotherapy? Who benefits?

Outstanding needs

- Predictive biomarkers for aggressive disease, treatment response, intermediate endpoints
- New imaging techniques

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Urinary Diversion

Sia Daneshmand, M.D.
Director of Urologic Oncology
USC Institute of Urologic Oncology



- Relevant Disclosures:
None

Urinary Diversion at USC



- Orthotopic diversion is arguably the gold standard
- Every patient undergoing radical cystectomy is considered for an orthotopic diversion, except when one or more contraindications apply.

SEER Data



Likelihood of continent diversion: (multivariate analysis)

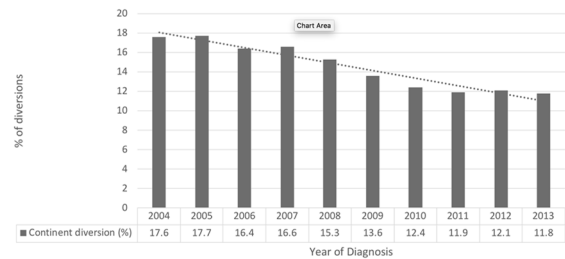
- Inversely associated with
 - **older age**
 - African American race
 - higher comorbidity index
- Directly associated with
 - male sex
 - higher education level
 - year of surgery
 - academic and NCI-designated cancer centers
 - high-volume providers

Frequency of urinary diversion by continent reconstruction versus ileal conduit in selected series

AUTHOR	n	YEARS	SERIES	CONT	IC	OTHER**
Stein et al (2001)	634	1987-1997	Univ. Southern California	93%	7%	0
Novotny et al (2006)	516	1993-2005	Technical Univ., Dresden, Germany	36.8%	57.9%	5.2%
Kouba et al (2007)	102	2004-2005	Univ. North Carolina	33%	67%	0
Gonheim et al (2008)	2,720	1970-2000	Urology and Nephrology Ctr., Mansoura, Egypt	73%*	25%	2%
Daneshmand (2009)	188	2004-2008	Oregon Health & Science Univ.	64%	35.5%	0.5%
Gore et al (2006)	3,611	1992-2000	Nationwide. Medicare, SEER	19.9%	80.1%	0
Gore et al (2008)	5,075	1998-2005	Nationwide. HCUP-NIS	14.3%	85.7%	0



Trends in continent diversion in the US from 2004-2013



Form the National Cancer Database (NCDB)



Factors influencing the choice of urinary diversion in patients undergoing radical cystectomy

Matt S. Ashley and Siamak Daneshmand
Section of Urologic Oncology, Oregon Health & Science University, Portland, OR, USA
 Accepted for publication 6 November 2009



- Of the **149 patients** eligible for a CUD, only nine (6%) chose to undergo ICUD for **personal reasons**
- Proper patient selection and thorough, standardized preoperative counseling result in a higher rate of CUD



Urologic Oncology: Seminars and Original Investigations 29 (2011) 473–475

News and topics

Choosing the right urinary diversion: Patient's choice or surgeon's inclination?

E.C Skinner, M.D.

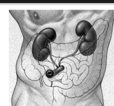


- "At least 2/3 of patients presenting for cystectomy are likely to be reasonable candidates for some sort of continent urinary diversion.
- "The vast majority of patients will opt for a continent diversion if the pros and cons of each type of diversion are presented in a balanced manner

Patient/Urinary Diversion Selection



- **Advantages** of Ileal Conduit Urinary Diversion
 - Shorter operative time
 - Ease of care by others
 - Easier to learn
- **Disadvantages**
 - Requirement of external appliance
 - Impairment of body image
 - Hernia
 - Skin irritation



Contraindications for Orthotopic Neobladder



- Compromised renal function (Cr >1.8, Cr clearance >45)
- Severe hepatic dysfunction
- Compromised intestinal function
- Positive urethral margin
- Mental impairment
- Pre-existing incontinence
- Pelvic radiation (increased complications)
- Recurrent urethral stricture disease
- **AGE NOT CONTRAINDICATION!!**

Renal Function



- 168 total cases
 - 44 - Ileal conduit
 - 109 - Studer orthotopic ileal neobladder
 - 15 - Continent cutaneous diversion
 - right colon pouch via Monti or appendico-umbilicostomy
- Pre-existing renal insufficiency (RI) vs. normal:
 - 58 – with insufficiency (eGFR < 60 ml/min)
 - 110 – normal

B Winters, J Cai, S Daneshmand. Short-term change in renal function in patients undergoing continent vs. noncontinent urinary diversions. UroToday Int J, 2013

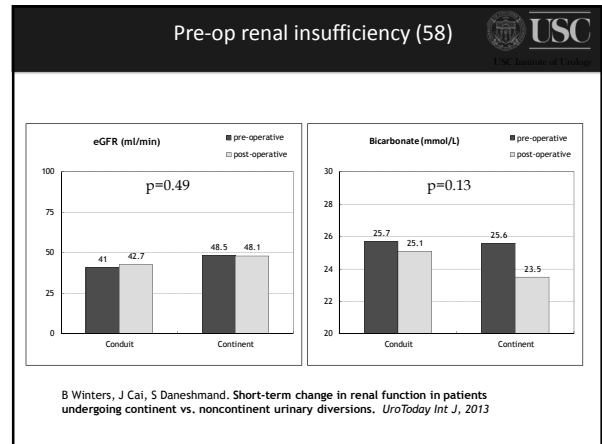
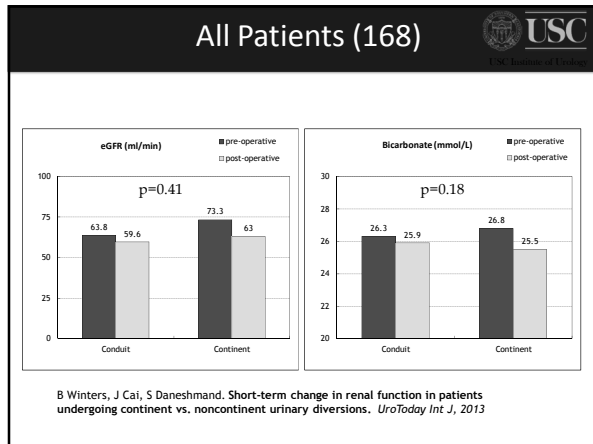
Renal Function



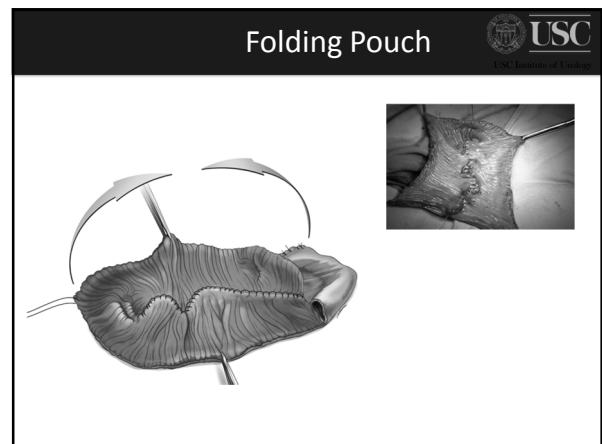
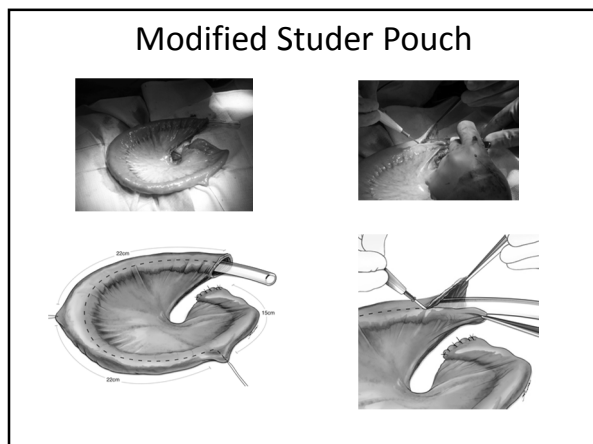
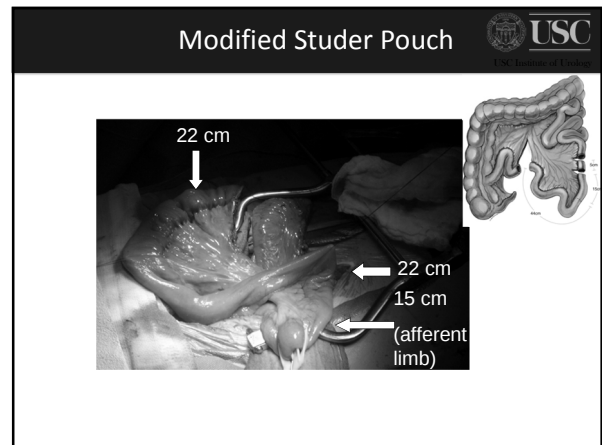
B Winters, J Cai, S Daneshmand. Short-term change in renal function in patients undergoing continent vs. noncontinent urinary diversions. UroToday Int J, 2013

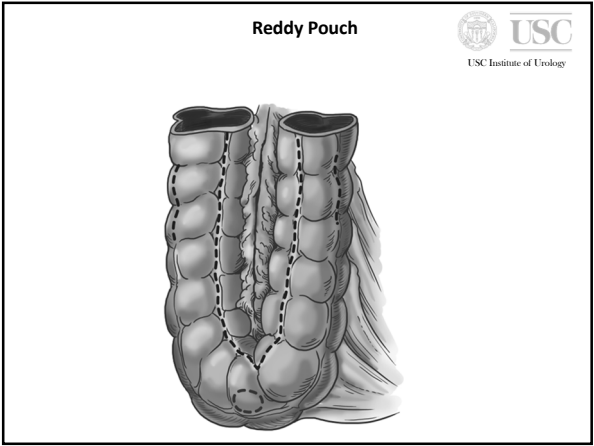
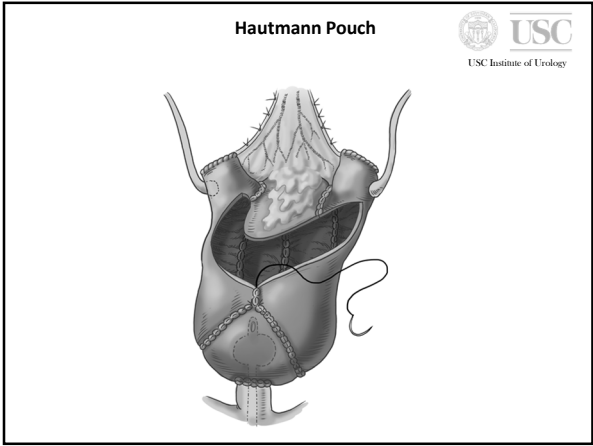
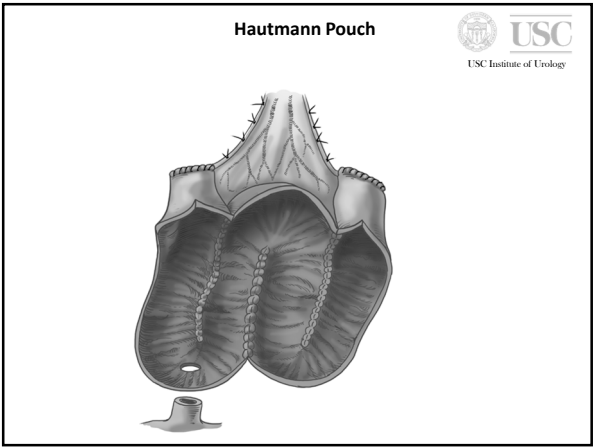
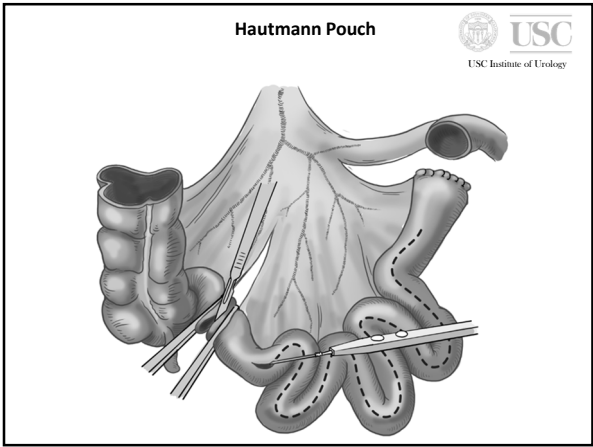
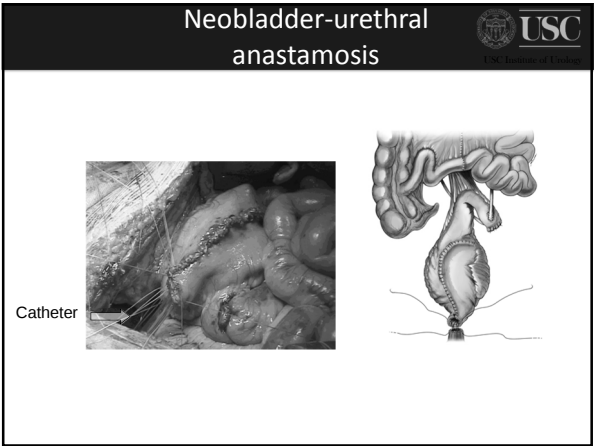
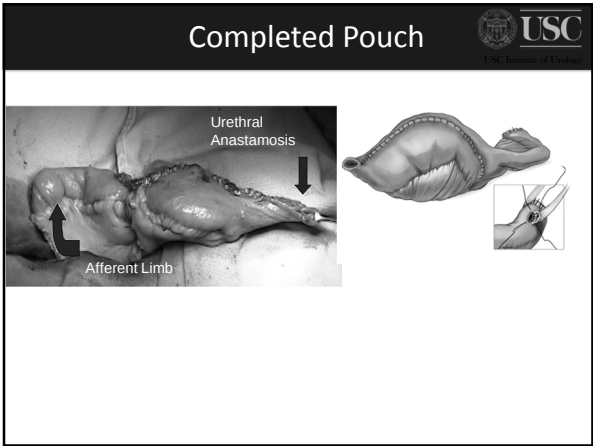
Summary table	Conduit	Continent	Significance
Average Age	71.4	65.3	p<0.001
Mean pre-op eGFR	63.8	73.3	p<0.001
Preexisting RI (58)	24 (41%)	34 (59%)	
Mean pre-op eGFR with Renal insufficiency	41	48.5	p=0.009
	Conduit	Continent	
Mean f/u for all	17.5	19.9	p=0.10
Median f/u for all	16 months (range 3-60)		

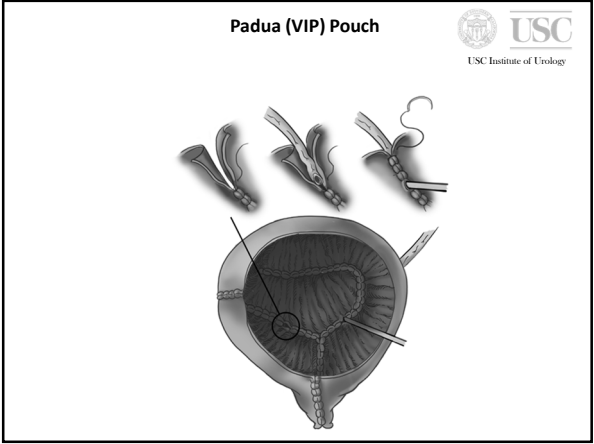
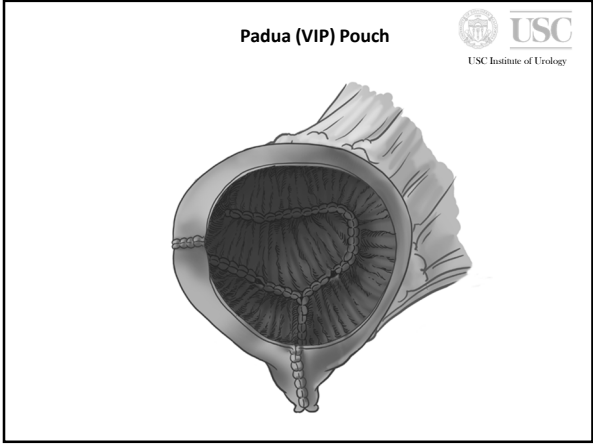
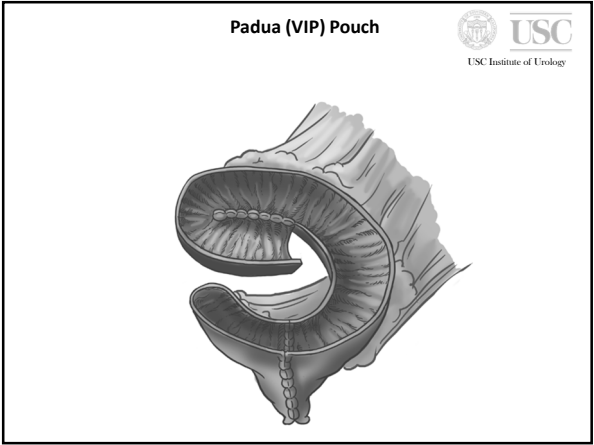
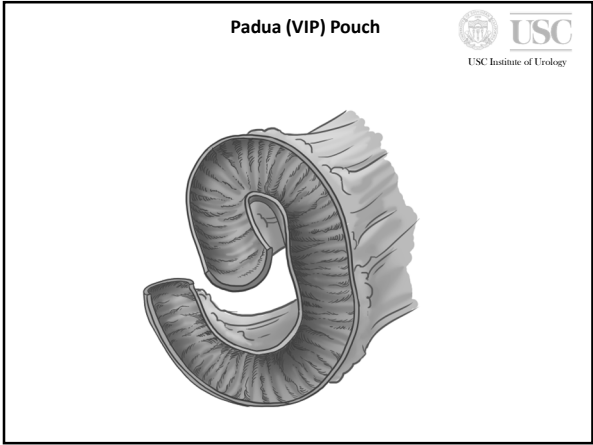
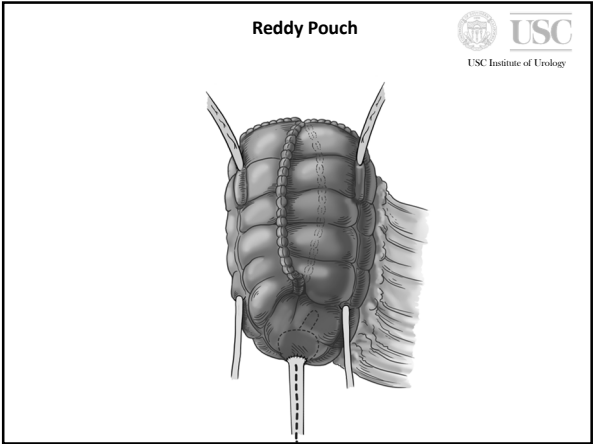
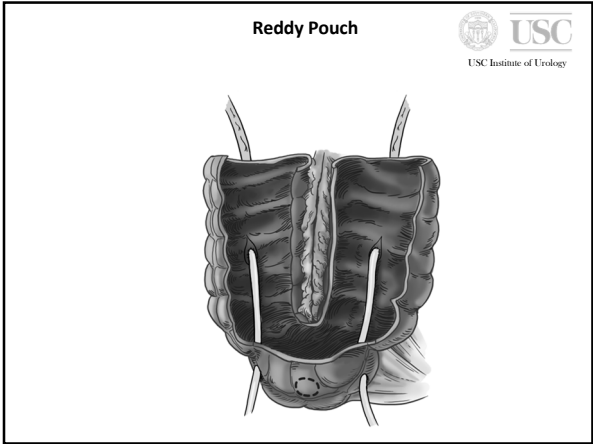
B Winters, J Cai, S Daneshmand. Short-term change in renal function in patients undergoing continent vs. noncontinent urinary diversions. UroToday Int J, 2013

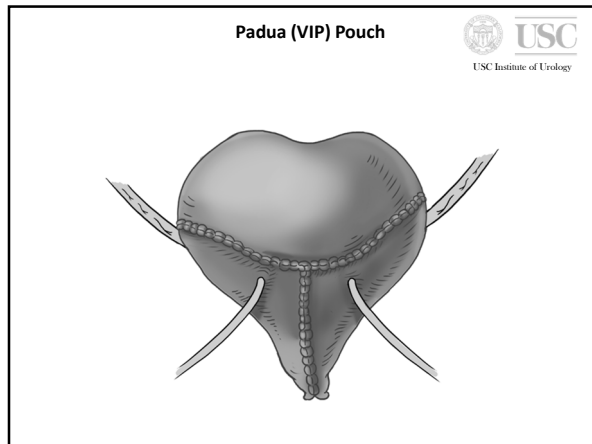


- ### Orthotopic Urinary Diversion
- Most common orthotopic diversions:
 - Studer pouch
 - Hautmann pouch









Patient/Urinary Diversion Selection

The “Truth” regarding

- Continence Rates
- Complication Rates
- Reoperation Rates

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Complication and Reoperation Rates with Orthotopic Neobladders

Authors/Year	No. of Patients	Mean Follow Up (months)	Ileal Neobladder Type	Early Complication Rate/Reoperation (%)	Late Complication Rate/Reoperation (%)	Hypercontinence at 1 year (%)
Hautmann et al./1999	363	57	Hautmann	39/26	32/30	4
Steven et al./2000	166	32 (Median)	Kock	24/15	37/32	33 (at 3 years)
Abol-Enein et al./2001	344	38	Hautmann	15/NR	10/NR	3 (all female)
Lee et al./2003	130	20	Studer (93) Hautmann (37)	14/NR	29/NR	9
Stein et al./2004	209	33 (Median)	T-Pouch	30/3	32/15	25 (20% of men, 43% of women)
Studer et al./2006	482	32 (Median)	Studer	32/7	55/28	3

NR: Not reported

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In the Literature....

Authors/Year	No. of Patients	Mean Follow Up (months)	Ileal Neobladder Type	Method of Data Collection
Hautmann et al. 1999	363	57	Hautmann	Retrospective
Steven et al. 2000	166	32 (Median)	Kock	Retrospective
Abol-Enein et al. 2001	344	38	Hautmann	Retrospective
Lee et al. 2003	130	20	Studer (93) Hautmann (37)	Retrospective
Stein et al. 2004	209	33 (Median)	T-Pouch	Retrospective
Studer et al. 2006	482	32 (Median)	Studer	Retrospective

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Prospective Evaluation of Continence Following Radical Cystectomy and Orthotopic Urinary Diversion Using a Validated Questionnaire

THE JOURNAL OF UROLOGY®

Thomas G. Clifford, Swar H. Shah, Soroush T. Bazargani, Gus Miranda, Jie Cai, Kevin Wayne, Hooman Djaladat, Anne K. Schuckman and Siamak Daneshmand*

- Mailed questionnaire to patients 12 or months after surgery
- 68% response rate
- Patient reported (vs. mostly surgeon assessed studies)

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Pad Usage Form

DATE: _____
 DOB: _____
 DDD: _____
 DDDU: _____

PATIENT STICKER

1. Do you wear pads?
☐ Yes ☐ No

2. How many pads per day do you typically wear?
 Daytime: ☐ 1-2 pads ☐ 3-4 pads ☐ 5 or more pads
 Nighttime: ☐ 1-2 pads ☐ 3-4 pads ☐ 5 or more pads

3. When do you wear them?
☐ Day only ☐ Night only ☐ Day and Night

4. Which pad size do you typically wear at:
 Daytime: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18 ☐ 19 ☐ 20
 Nighttime: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18 ☐ 19 ☐ 20

5. How wet are your pads when you change them?
 Daytime: ☐ Almost dry ☐ Slightly wet ☐ Wet ☐ Soaked ☐ Too variable to classify
 Nighttime: ☐ Almost dry ☐ Slightly wet ☐ Wet ☐ Soaked ☐ Too variable to classify

6. Do you leak mucus? If yes, how often do you leak mucus? (Circle one number)
 Every day: _____
 About once a week: _____
 Less than once a week: _____
 Not at all: _____

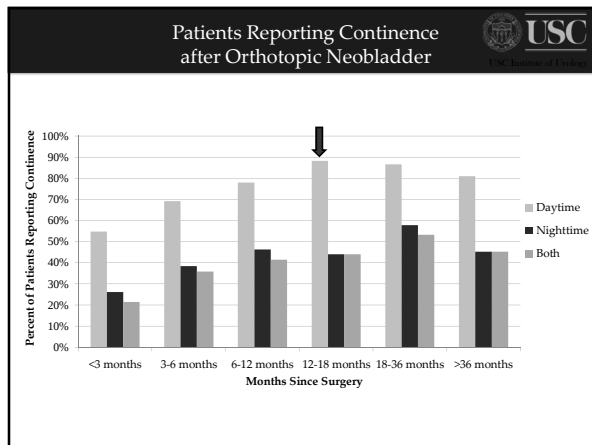
7. Do you catheterize?
☐ Yes ☐ No

8. How many times a day do you catheterize?

Updated 9/2014

Results

- Forms collected from patients followed in the clinic from August 2012 to October 2014
- Patients underwent RC between 2000 and 2014 – 1545 patients
- 153 male patients with available questionnaires
- 284 pad usage questionnaires were collected
- 243 interval distinct questionnaires were defined



Results

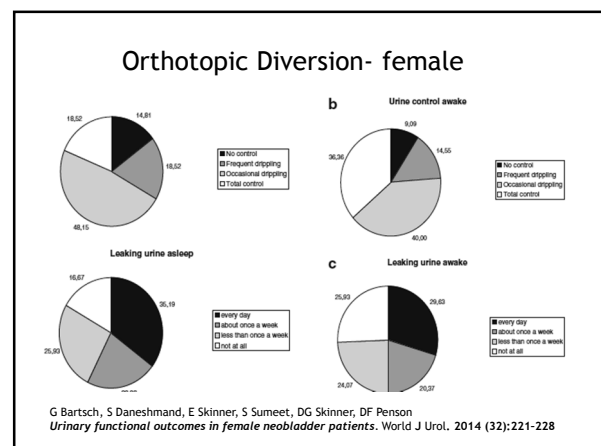
- Overall catheterization rate in the cohort was 13%
- Median time to catheterization was 15.9 months

ORIGINAL ARTICLE

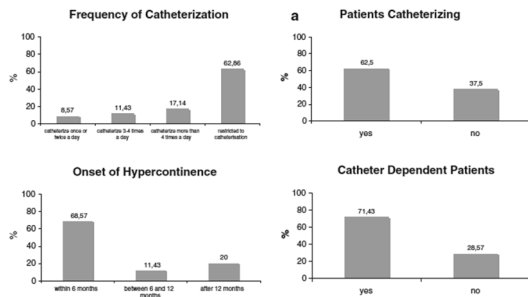
Urinary functional outcomes in female neobladder patients

Georg Bartsch · Siamak Daneshmand ·
 Ella C. Skinner · Sumeet Syan ·
 Donald G. Skinner · David F. Penson

World Journal of Urology



Orthotopic Diversion- female



G Bartsch, S Daneshmand, E Skinner, S Sumeet, DG Skinner, DF Penson
Urinary functional outcomes in female neobladder patients. World J Urol. 2014 (32):221-228

Functional outcomes in women

Table 4 Functional outcomes in women undergoing IC and orthotopic reconstruction.

Reference	Number of women	Median follow-up, months	Continence rate, % or n/N	Catheterisation, % or n/N	Continent during day and night, % or n/N
Ali et al, 2002 [4]	60	39	93	84	14
Araki, Y, 1999 [28]	12	33	10/12	6/12	4/12
Hautmann, R, 2009 [29]	42	NR	86*	NR	47
Naal, A, 2001 [30]	102	24	82	72	12
Shaw, L, 2002 [31]	88	30	75-78***	NR	44-58*

NR, not reported; *Percentage of patients reporting continence both during the day and at night; **Range based on chart review and patient questionnaire.

RK Lee, HA Enin, W Artibani, B Bochner, G Dalbagni, S Daneshmand, Y Fradet, RE Hautmann, CT Lee, SP Lerner, A Pycha, KD Sievert, A Stenzl, G Thalmann, SF Shariat. *Urinary diversion after radical cystectomy for bladder cancer: options, patient selection, and outcomes.* BJU Int 2014; 113: 11-23.

Orthotopic Diversion in Females

AUTHOR	TYPE OF RESERVOIR	NO. OF PATIENTS	MEAN FOLLOW-UP (mo)	MEAN AGE (yr)	MORTALITY Y (%)	COMPLICATIONS*		CONTINENCE			IC (%)	ANTIREFLUX MECHANISM
						EARLY (%)	LATE (%)	DAY (%)	NIGHT (%)			
Isaacs et al (2003)	Ileum	102	26	59	0	5	12	82	72	12		None
Granberg et al (2008)	Ileum (Studer)	59	29	62	0	22	5	90	57	35		None
Ali-Ei-Din et al (2008)	Ileum, serous-lined extramural tunnel	192	51	54	2	16	35	92	72	16		Serous-lined extramural ureter
Stein et al (2009)	Ileum (Studer or T pouch)	120 (n = 56 for continence results)	103	66	2.5	32	26	77	66	61 (59% dependent on IC to void)		T pouch 45%
Isentz et al (2012)	Ileum (Hautmann)	131	56	61	1.7	16	NA	82.4	75.9	58		None
Anderson et al (2012)	NA	49	37	60	NA	NA	NA	57	45	31		NA
Bartsch et al (2014)	Ileum (Studer or T pouch)	56	63	64	NA	NA	NA	30	35	62 (45% dependent on IC to void)		NA

*Complications reported related to urinary diversion; definitions vary by report.

†Continence results from validated patient-completed questionnaires.

IC, intermittent catheterization to empty neobladder; NA, not available from report.

Ileal Conduit Outcomes

- Madersbacher et al. (J Urol 2003, 169:985-90)
 - Retrospective analysis 382 patients who underwent ileal conduit urinary diversion
 - Minimum follow-up 5 years
 - Mean follow-up >8 years
- Long term conduit-related complication rate: 66%
- 11% required reoperation
- Most common complications (2.2 mean complications/patient)
 - Renal 27%
 - Stomal 24%
 - Bowel 24%
 - Infection 23%
 - Uretero-ileal/conduit fibrosis 14%

Quality of Life Studies on Urinary Diversion

- Extensive literature, generally low scientific quality
- Published evidence
 - No difference in QOL when comparing:
 - Continent cutaneous and conduit
 - Neobladder and conduit
 - Continent cutaneous and neobladder
 - Neobladder, continent cutaneous, and conduit
 - Difficult study design

Patient/Urinary Diversion Selection

- Patient must ultimately weigh the given risks and benefits based on:
 - Lifestyle
 - Motivation
 - Priorities

Summary of comparative urinary diversion HRQOL studies since 2000					USC
References	Instrument	No. Pts	Year	Population	Findings
McGuire et al	SF-36	76	2000	United States	Lower mental QOL scores in IC patients compared to population norm
Refsum et al	SF-36	56	2000	Japan	No differences detected between groups
Webb et al	EORTC QLQ-C30	102	2000	Austria	Higher QOL scores in NB patients
Hara et al	SF-36 + informal questionnaire	85	2002	Japan	No differences detected in general HRQOL
Datta et al	SF-36 FACT-G	100	2002	United States	Marginally higher HRQOL scores detected in NB group
Protogerou et al	EORTC QLQ-C30, informal questionnaire	108	2004	Greece	Urinary and sexual function impairments present following cystectomy but no HRQOL differences between groups
Kikuchi et al	FACT-BL	35	2006	Japan	Lower body image scores among ileal conduit patients
Gilbert et al	BCI	115	2007	United States	Decreased urinary HRQOL among NB group
Saika et al	EORTC QLQ-C30	78	2007	Japan	No significant difference between IC and NB
Autorino et al	SF-36	79	2008	Italy	No difference between IC and NB, but physical, emotional and social QOL scores below population norm
Soppi et al	EORTC QLQ-C30 + EORTC QLQ-BLM30	34	2008	Italy	Global health status higher in NB group but not significant
Philip et al	SF-36, informally developed questionnaire	52	52	England	NB group had significantly better physical functioning
Somani et al	EORTC QLQ-C30 + SWLS	32	2009	England	No HRQOL difference before or after cystectomy
Hedberg et al	BCI	224	2010	United States	No difference between IC and NB groups
Ehner et al	EORTC QLQ-C30 + EORTC QLQ-BLM30	58	2012	Germany	Higher HRQOL scores among NB vs. IC patients
Gucci et al	EORTC QLQ-C30 + EORTC QLQ-BLM30, FACT-BL	25	2013	Italy	No HRQOL differences among female patients
Metcalf et al	FACT-V01	84	2013	Canada	No HRQOL differences between IC and NB groups
Singh et al	EORTC QLQ-C30	164	2014	India	General HRQOL better in NB group compared to IC group
Huang et al	BCI	294	2015	China	No difference in long-term HRQOL between IC and NB

Summary

- Patient/Urinary Diversion Selection
 - Provide patient with realistic expectations by informing them of continence and complication expectations
- Evidence does not support use of mechanical bowel prep (Limited evidence in the urologic literature)
- Only ≤ 24 hr dose of prophylactic antibiotics necessary
- Intra-operative stenting of uretero-intestinal anastomosis likely beneficial

Necessity of Mechanical Bowel Prep

- Guenaga et al. Cochrane Database of Systematic Reviews 2005, Issue 1
 - Systematic review involving 9 trials, 1592 patients to determine effectiveness and safety of prophylactic mechanical bowel prep in elective colorectal surgery
 - **No evidence to show mechanical bowel prep reduces anastomotic leak**
 - No difference in
 - Mortality
 - Morbidity
 - Peritonitis
 - Re-operation
 - Surgical site infection
 - Some evidence to suggest mechanical bowel prep may increase rate of anastomotic leakage and wound complications

Necessity of Nasogastric Tube

- Inman et al. J Urol (2003); 170:1888-1891
 - Retrospective evaluation of 420 patients undergoing radical cystectomy and urinary diversion, NGT placed at discretion of surgeon
- Patients without NGT:
 - Significantly shorter time to first flatus
 - Significantly shorter duration of hospitalization
 - No increased risk of ileus, bowel obstruction, wound dehiscence, anastomotic leak, or aspiration pneumonia

ERAS following radical cystectomy and urinary diversion

- Evidence-based protocol in perioperative care of patients who undergo cystectomy and urinary diversion.
- Goals
 - Primary:
 - 1) Decrease LOS without increasing readmission rate.
 - 2) Minimize early complications.
 - Secondary:
 - 1) Improve patient experience
 - 2) Decrease ileus rate

Peri-operative management protocol

Pre-operative:

- 24-hr perioperative antibiotic
- Home IV hydration
- Prophylactic antibiotic
- Oral sodium bicarbonate at time of discharge
- Pre-Cx educational class
- Carbohydrate loading
- No bowel prep
- Alvimopan
- No epidural

Intra-operative:

- No NGT
- Nausea & Vomiting prophylaxis
- Alvimopan
- Neostigmine
- H₂ blocker and PPI
- Early enteral feeding
- Non-narcotic pain control
- Opioid-sparing anesthesia
- Minimize IV fluid based on stroke-volume

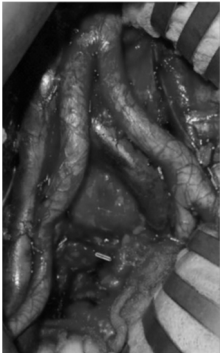
Post-operative:

- 24-hr perioperative antibiotic
- Home IV hydration
- Prophylactic antibiotic
- Oral sodium bicarbonate at time of discharge
- Pre-Cx educational class
- Carbohydrate loading
- No bowel prep
- Alvimopan
- No epidural
- Opioid-sparing anesthesia
- Minimize IV fluid based on stroke-volume

ERAS

- Smaller incision
- Less bowel manipulation and efficient and expeditious surgery
- Minimization of blood loss and transfusion
- Consistency

SWOG S1011 “Extended Lymph node dissection”



“super extended PLND”



ERAS

Preservation of gastrointestinal function

- Carbohydrate loading.
- Pharmacological prophylaxis of postoperative nausea or vomiting
- Avoidance of NG tubes
- Avoidance of bowel preparation
- Enforced early enteral feeding- “cystectomy” diet on POD#1
- Liberal use of laxatives.
- Alvimopan

ERAS

Active pain control

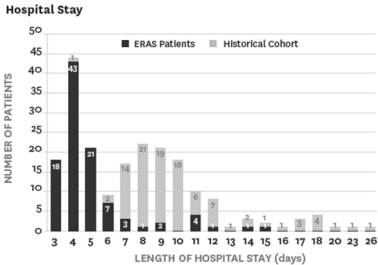
1. Non-narcotic analgesia initiated intraoperatively.
2. Opioids for breakthrough pain
3. Instillation of local anesthetic catheters at incision sites.

Enhanced Recovery Protocol after Radical Cystectomy for Bladder Cancer

THE JOURNAL OF UROLOGY

Siamak Daneshmand,*† Hamed Ahmadi, Anne K. Schuckman,‡ Anirban P. Mitra, Jie Cai, Gus Miranda and Hooman Djaladat

From the Institute of Urology, Norris Comprehensive Cancer Center and Department of Pathology and Center for Personalized Medicine (APM), University of Southern California, Los Angeles, California



USC ERAS (Updated results)

Patients	USC-ERAS Open RC (2012–2014)	STAR trial (2002–2009)	USC modern era (2003–2009)
No. (M/F)	377 (169/52)	484 (411/73)	557 (433/124)
Age	69 (31-90)		
Neoadjuvant chemo	98 (35%)		
Diversion type	ONB: 173 (62%) CCD: 14 (7%) IC: 75 (34%)	ONB	ONB: 448 (80%) CCD: 23 (5%) IC: 85 (15%)
EBL (median)	400 cc		
Median time to BM (d)	2		
Median LOS (d)	4 (3-24)	8 (0-70)	9 (4-62)



90 day Complication categories, ER visits and readmissions

Category	ERAS	Controls	p-value
Dehydration	14.2%	9.3%	0.22
Wound	11.8%	20.4%	0.05
Thromboembolism	7.7 %	9.3%	0.21
Infection	32.0%	41.7%	0.10
Cardiovascular	11.8%	13.9%	0.62
Pulmonary	4.1%	4.6%	0.85
Gastrointestinal	21.3%	33.3%	0.03
Renal/Metabolic	17.2%	23.1%	0.22
Neurologic	1.2%	1.9%	0.65
Hematological	25.4%	17.6%	0.13
Other	13.0%	7.4%	0.14
Death	4.1%	4.6%	0.85
Total	132 (78.1%)	86 (79.6%)	0.76
ER Visit (%)	64 (37.9%)	38 (35.2%)	0.65
Readmission (%)	50 (29.6%)	29 (26.9%)	0.62

**Postoperative Pain Management after Radical Cystectomy:
Comparing Traditional versus Enhanced Recovery Protocol
Pathway**

Weichen Xu, Siamak Daneshmand, Soroush T. Bazargani, Jie Cai,
Gus Miranda, Anne K. Schuckman and Hooman Djaladat*

From the Institute of Urology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California

	ERAS	Traditional	p-value
Total number of patients	124	81	
Median age (years)	71	70	0.6
Female sex (%)	27 (21.8)	18 (22.2)	1
Charlson comorbidity index (number of pts)			
0	56	39	
1	27	20	
≥2	41	23	0.7
Pathologic organ confined cancer (%)	79 (63.7)	52 (64.2)	1
Median surgery length (min)	350	360	0.2
Median estimated blood loss (mL)	400	600	0.0001
Length of hospital stay (day)	4	8	<0.0001
Mean morphine equivalent use (mg/day)	4.9	20.67	<0.0001
Total morphine equivalent use (mg)	24.08	102.48	<0.0001
Mean pain VAS score/ day	3.1	1.14	<0.0001
Postoperative ileus (%)	9 (7.3)	18 (22.2)	0.0028

J Urol, Vol. 194, 1209-1213, November 2015

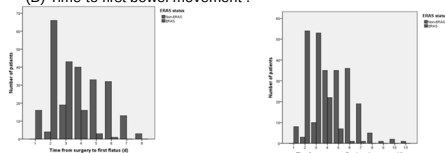
**USC ERAS
Complications/Readmissions**

	USC-ERAS (2012-2014) Prospective	STAR trial (2002-2009) Retrospective
Readmission rate (30 days)	44 (20%)	
• Dehydration	18 (8.6%)	107 (22.1%)
• UTI	20 (9%)	
• Postoperative ileus	7 (2.3%)	
Complication (30 days)	130 (59%)	271 (56%)
Major complications Clavien (3-5)	33 (15%)	

Table 1. GI-related complications in patients on
ERAS protocol vs. matched non-ERAS

	ERAS patients (n=145)	Non-ERAS controls (n=144)	P value
30-day GI complication rate (%)	19 (13)	40 (27)	0.003
Ileus/pSBO (%)	10 (7)	34 (23)	<0.001
Intractable nausea/vomiting (%)	4 (3)	3 (2)	0.5
Intractable diarrhea (%)	1 (<1)	1 (<1)	NA
Intractable constipation (%)	1 (<1)	-	NA
C. Diff diarrhea (%)	3 (2)	1 (<1)	0.3
30-day readmission rate due to GI complication (%)	2 (10)	2 (5)	0.1

Figure 1. Comparison between ERAS patients
and controls with regard to (A) Time to first flatus
(B) Time to first bowel movement.


Continent Cutaneous Diversion

Patient/Urinary Diversion Selection



- Advantages of continent cutaneous urinary diversion
 - High total (day and night) continence rate
 - Immediate continence
 - No need for external appliance
- Disadvantages of a continent cutaneous urinary diversion
 - Need for regular catheterization
 - Risk for reoperation for complications

Continent Cutaneous Diversion



- Indications
 - Urinary Incontinence
 - Urethral stricture
 - Positive urethral margin
 - ? Prior Pelvic Radiation

Continence Mechanism



- Ileocecal Valve (Indiana Pouch)
- Tapered Ileum
- Appendix (buried in subserosal tunnel)

Continence Rates with Continent Cutaneous Urinary Diversions

Authors	Year	No. Pts	Mean Follow Up (mos)	Urinary Diversion Type	Daytime and Nighttime continence (%)
Bihrie R	1997	50	30 (minimum)	Indiana	94
Stein et Daneshmand	2004	27	33	Penn	100
Wiesner et al.	2006	401	95	Mainz I/Right Colon	87
Holmes et al.	2002	125	41	Indiana	72
Webster et al.	2003	74	133	Florida	93

Complication Rates with Continent Cutaneous Urinary Diversion

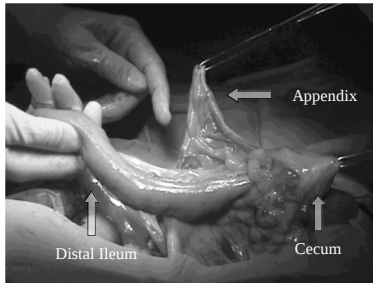
Authors	Year	No. Pts	Follow Up (mos)	Urinary Diversion Type	Complication Requiring Surgical Intervention (%)	Stomal Complications (% of total patients)
Bihrie R	1997	50	30 (minimum)	Indiana	18	6
Stein et Daneshmand	2004	27	33 (mean)	Penn	33	28
Wiesner et al.	2006	401	95 (mean)	Mainz I/Right Colon	> 51	36
Holmes et al.	2002	125	41	Indiana	52	14
Webster et al.	2003	74	133	Florida	39	12

Continence and Complications with Continent Cutaneous Urinary Diversion



- Continence
 - Complete Continence: 72-100%
- Complications Requiring Reoperation
 - 18-52%
 - Primarily stomal revisions, ureteral revisions, and pouch stones

Right Colon Pouch



Right Colon Pouch



Right Colon Pouch



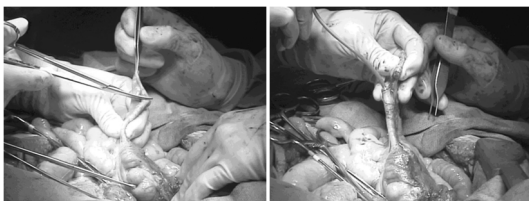
25cm segment of right colon isolated

Right Colon Pouch



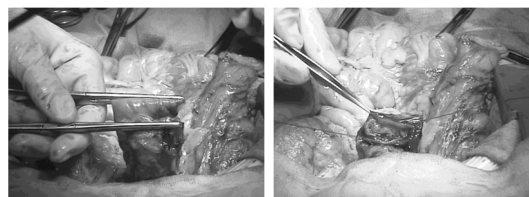
Isolated segment of bowel for pouch

Right Colon Pouch



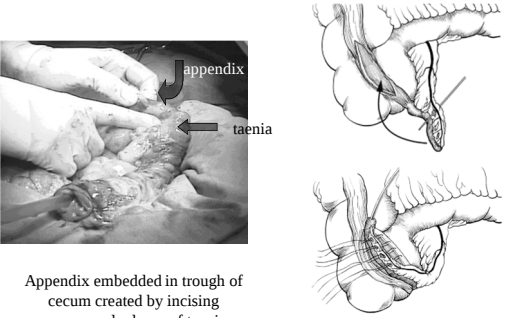
Appendiceal tip cut to allow 12-16F Catheter

Right Colon Pouch



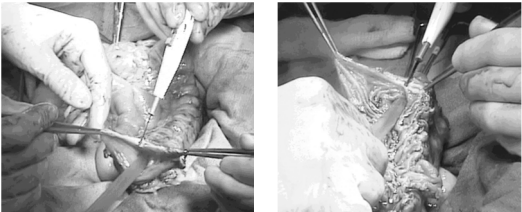
Two-layered hand sewn ileo-colic anastomosis

Right Colon Pouch



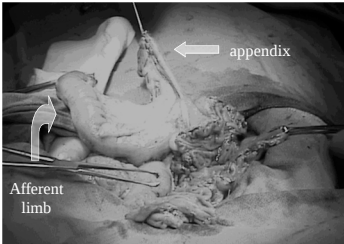
Appendix embedded in trough of cecum created by incising seromuscular layer of taenia

Right Colon Pouch



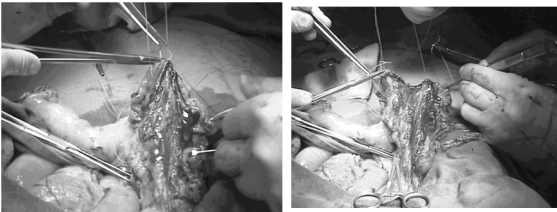
Colon opened toward cecum

Right Colon Pouch



Ileo-cecal valve serves as anti-reflux mechanism

Right Colon Pouch

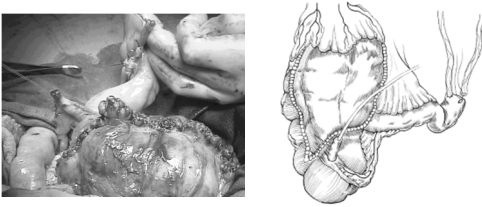


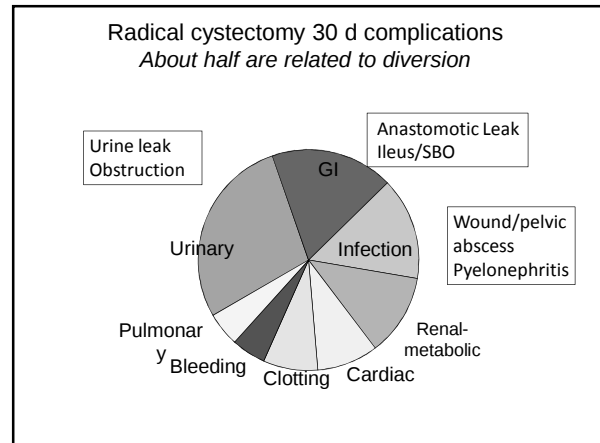
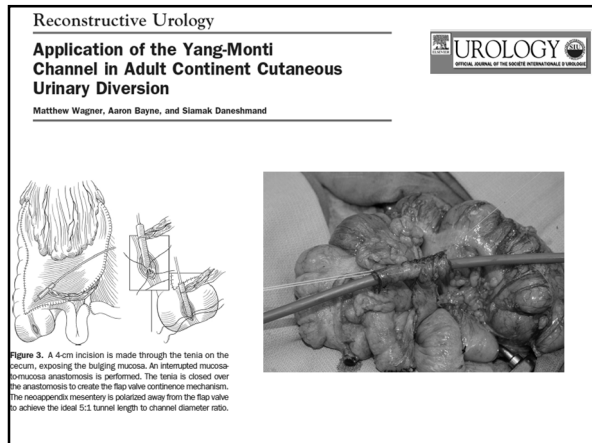
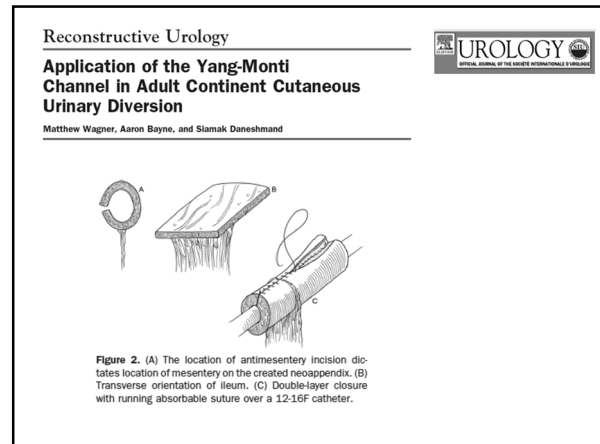
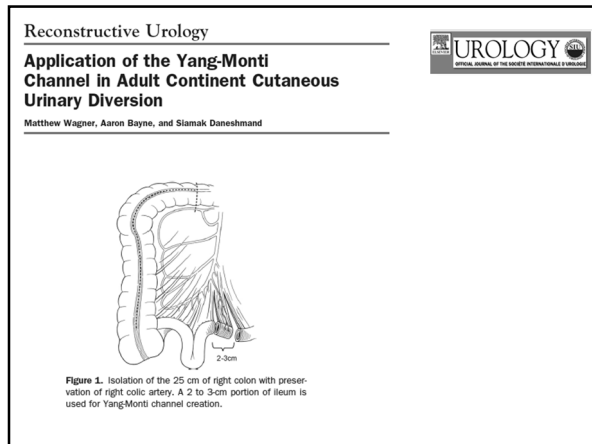
Colon folded on itself and sewn in 2 layers

Right Colon Pouch



Right Colon Pouch





USC

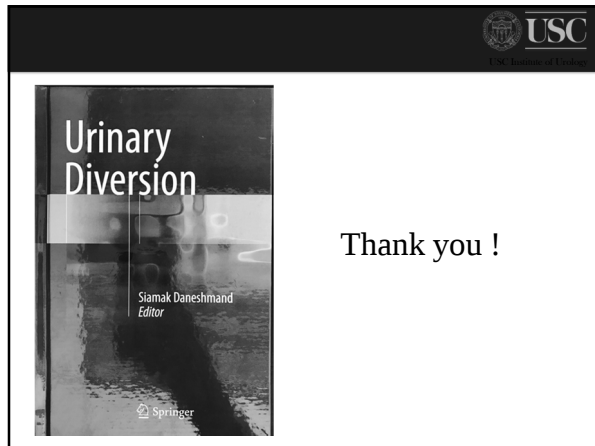
OUTLINE

- Early diversion-related complications management
 - GI complications
 - Urine leak
 - Pelvic abscess, infected lymphocele
 - UTI/sepsis
- Management of late complications by diversion type
 - Ureteroileal strictures
 - Parastomal hernia
 - Pouch stones
 - Incontinence
 - Difficulty catheterization/stoma stenosis

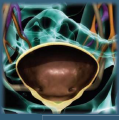
USC

Bowel Complications

- Most common early complication
- Most are not serious but are aggravating
- Can minimize with ERAS techniques
- Diarrhea/constipation/nausea
 - manage with OTC meds
 - rule out C.Diff if diarrhea persists > 2 d
 - may cause dehydration – require support/readmission
- Bowel anastomosis leak 1-2%
 - often subtle, difficult to diagnose
 - may lead to fistula, pelvic abscess, ureteral obstruction
 - Can avoid with careful technique
 - percutaneous drains, bowel rest
 - rarely need to re-operate except for severe leak, rectal injury or refractory SBO



Thank you !



Medical Management and Phenotyping BPH / LUTS Patients

Steven A. Kaplan, M.D.
Professor of Urology
Icahn School of Medicine at Mount Sinai
Director, Benign Urologic Health
Mount Sinai Health System

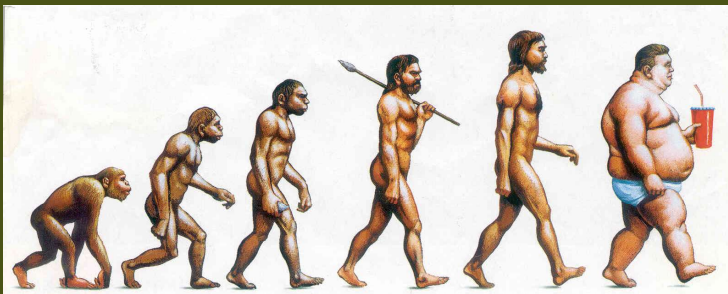
Disclosure:

Dr. Kaplan has nothing to disclose.



Male Pelvic Health New Terminology, New Concepts, Better Choices

- Significance of obesity and the metabolic syndrome

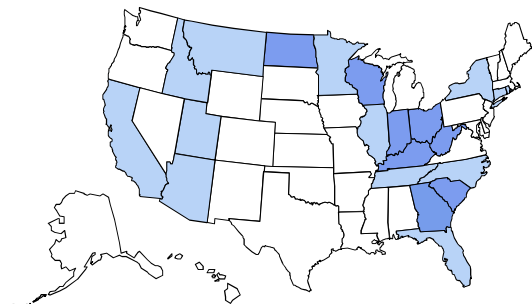


The Economist: The Shape of Things to Come, December 13-19, 2003



Obesity Trends* Among U.S. Adults BRFSS, 1985

(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



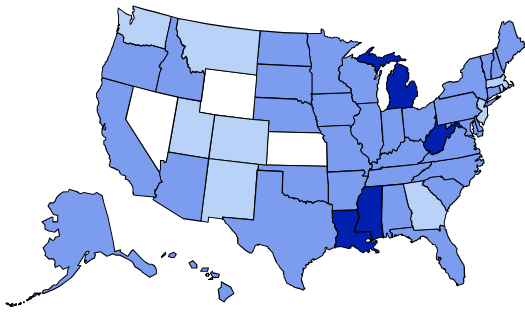
□ No Data ■ <10% ■ 10%-14%

Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults BRFSS, 1991

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

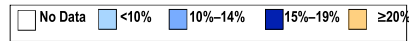
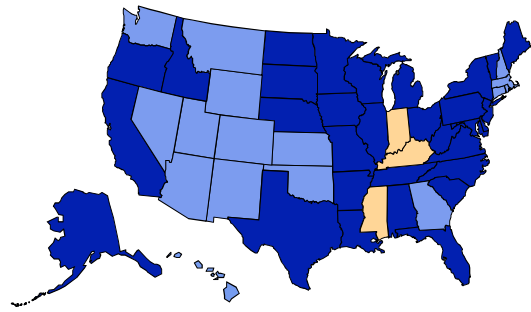


Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults BRFSS, 1997

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

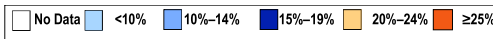
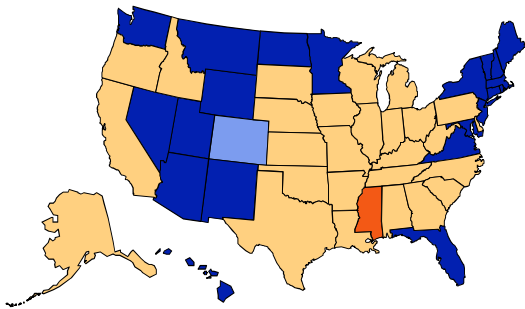


Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

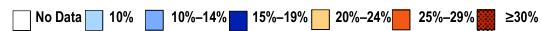
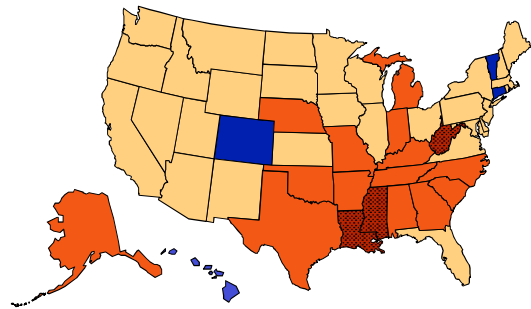


Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)

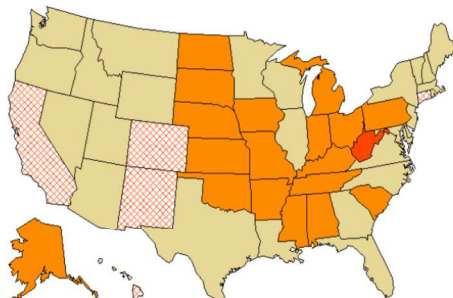


Source: Behavioral Risk Factor Surveillance System, CDC.



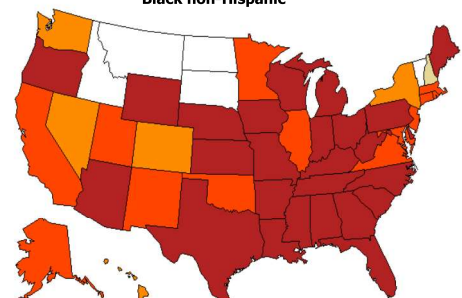
State-specific Prevalence of Obesity* Among U.S. Adults, by Race/Ethnicity, 2006-2008

White non-Hispanic

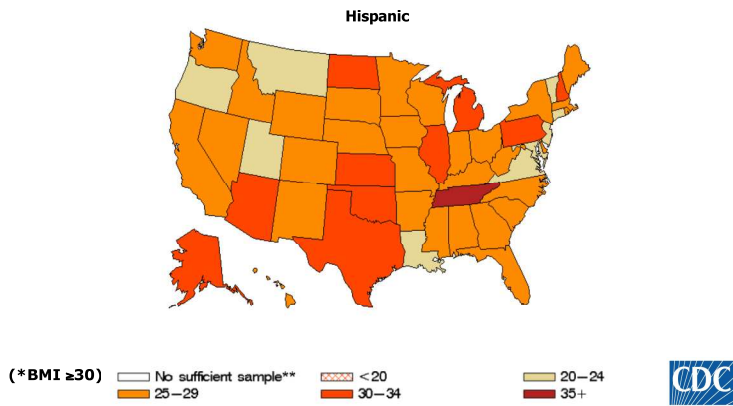


State-specific Prevalence of Obesity* Among U.S. Adults, by Race/Ethnicity, 2006-2008

Black non-Hispanic

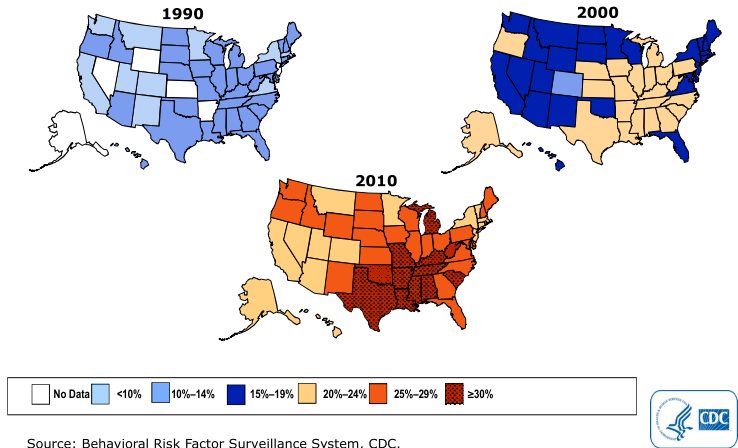


State-specific Prevalence of Obesity* Among U.S. Adults, by Race/Ethnicity, 2006-2008



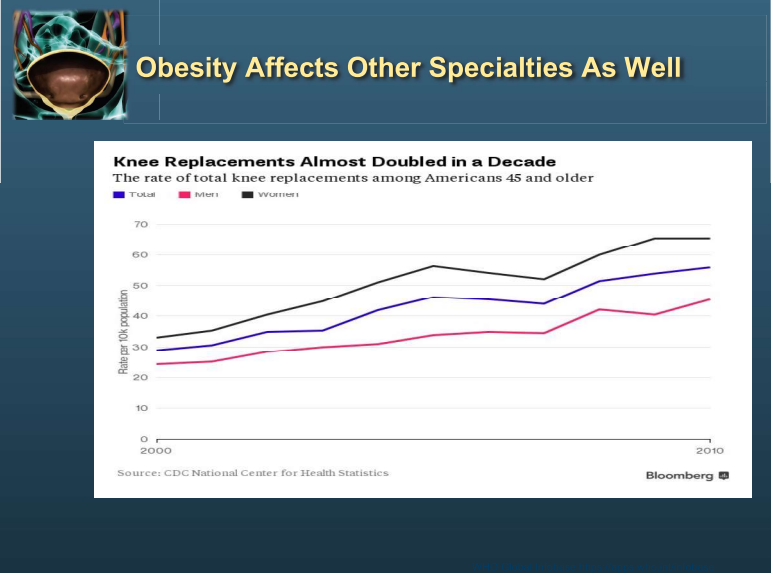
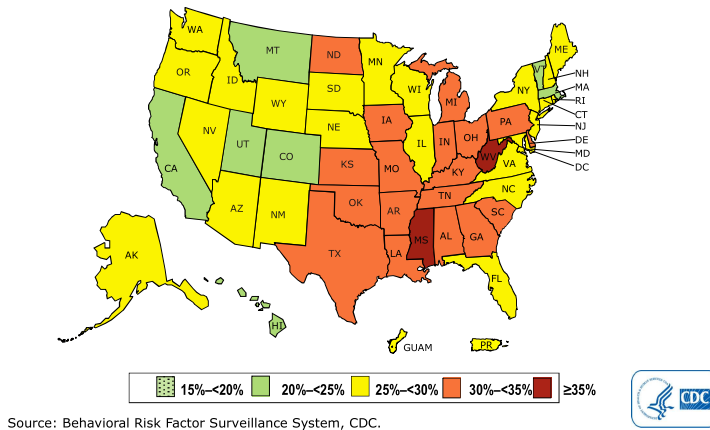
Obesity Trends* Among U.S. Adults BRFSS, 1990, 2000, 2010

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2013

*Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



Treatments for LUTS, BPH, BOO

- Watchful waiting^{1,2}
 - Medical therapy^{2,3}
 - Phytotherapy
 - α-adrenoreceptor (AR) blockers
 - 5-α reductase inhibitors
 - Antimuscarinic agents
 - PDE – 5 inhibitors
 - Combination therapy
 - Office-based treatment^{2,3}
 - TUMT (transurethral microwave thermotherapy)
 - TUNA (transurethral needle ablation)
 - Botulinum toxin type A injection
 - Experimental treatments
 - Surgicenter/hospital-based treatment^{2,3}
 - TURP (transurethral resection of the prostate; gold standard)
 - TUIP (transurethral incision of the prostate)
 - Open surgery (prostatectomy)
 - TUVP (transurethral electrovaporization ablation of the prostate)
- Phytotherapy
α-adrenoreceptor (AR) blockers
5-α reductase inhibitors
Antimuscarinic agents
PDE – 5 inhibitors
Combination therapy

1. Chatelain C et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:519-534.

2. McConnell JD et al. *Benign Prostatic Hyperplasia: Diagnosis and Treatment*. Baltimore, MD: Williams & Wilkins; 1994. AHCPR Publication No. 94-0582.

3. Dreikorn K et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:479-511.

Male LUTS

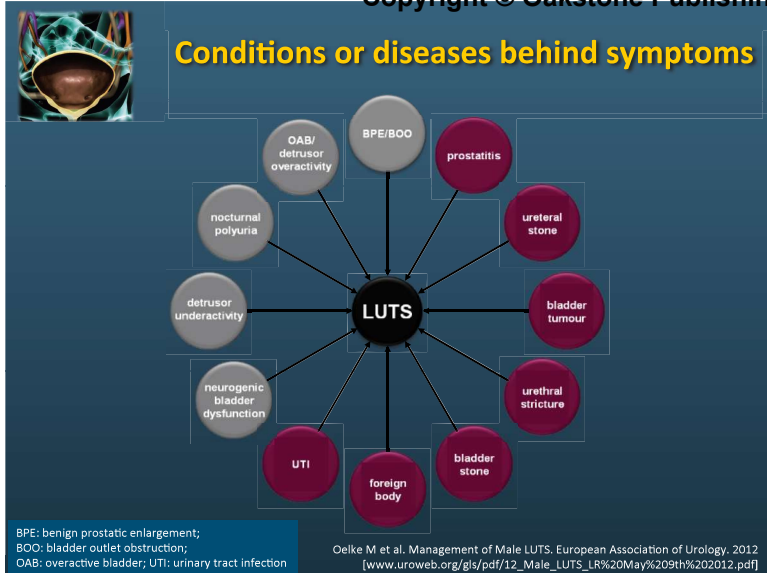
Identification of Patient Profile

–Who has BPH?

–Who should be treated?

–What is the optimal treatment for each patient?

Conditions or diseases behind symptoms



Pharmacological Options

Targeting the bladder

Antimuscarinics

→ Symptom control of OAB (storage) component of LUTS ↓ involuntary bladder contractions

PDE5 inhibitors (prostate ± bladder?)

Targeting the prostate

α-blockers

→ Symptom control by relaxation of prostatic and urethral tissue

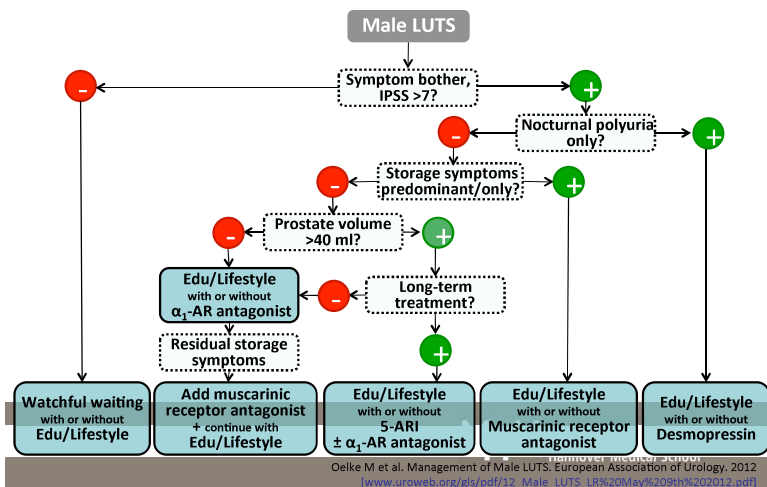
5-ARIs

→ Long-term symptom control and prevention of disease progression by prostatic tissue shrinkage

5-ARIs: 5α-reductase inhibitors; OAB: overactive bladder

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

Treatment Algorithm Male LUTS: Drugs



α-Blockers for Treatment of BPH

- Most commonly used and effective medical therapy for treating LUTS secondary to BPH¹
- Prevents clinical symptomatic progression of BPH¹
- Efficacious²
- Well tolerated
- Reduce the cost of medical therapy³

1. IMS HEALTH NPA 2008.

2. McConnell JD et al. *N Engl J Med.* 2003;349:2387-2398.

3. Naslund M et al. *Am J Manag Care.* 2007;13(suppl 1):S17-S22.

Efficacy of alpha1 - blocker

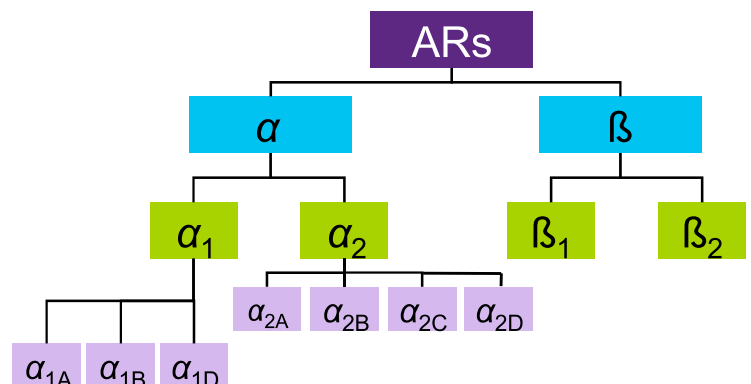
	α ₁ -AR antagonist
Total IPSS	↓ 35 - 40%
Q _{max}	↑ 20 - 25%
Onset of action	Rapid (days)
Prostate volume	-
Long-term risk of AUR or BPH-related surgery	-

AUR: acute urinary retention;
BPH: benign prostatic hyperplasia;
IPSS: International Prostate Symptom Score;
Q_{max}: maximum urinary flow rate

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

RAPAFLO
(silodosin) capsules

Adrenoreceptor (AR) Subtypes



Adapted from Roehrborn CG, Schwinn DA. *J Urol.* 2004;171:1029-1035.

α_1 Adrenoreceptor Distribution & Function



α_{1A}

Primary subtype expressed in the prostate. Regulates contraction of the smooth muscle in the prostate, bladder base and neck, urethra, seminal vesicles, and vas deferens.¹⁻⁵

α_{1D}

Primary subtype expressed in the bladder, spinal cord, and nasal passages. Thought to play a role in bladder symptoms. Regulates nasal secretions.^{1,6}

α_{1B}

Primary subtype expressed in the blood vessels in response to postural redistribution of blood volume.⁴⁻⁷

1. Schwinn DA, et al. *Int J Urol*. 2008;15:193-199.

2. Kaplan SA. *Urology*. 2004;63:428-434.

3. Nasu K, et al. *Br J Pharmacol*. 1996;119:797-803.

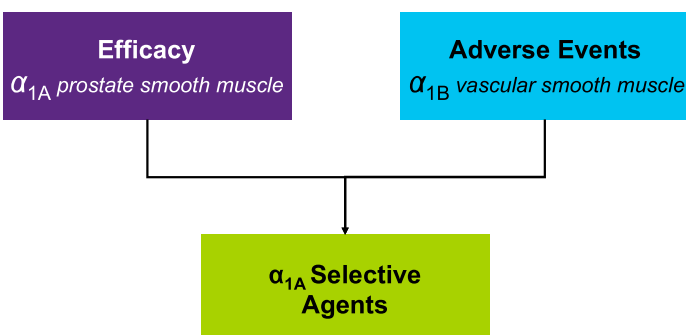
4. Murata S, et al. *J Urol*. 2000;164:578-583.

5. Carbone DJ, et al. *Int J Impotence Res*. 2003;15:299-306.

6. Stafford-Smith M, et al. *Can J Anesth*. 2007;54:549-555.

7. Townsend SA, et al. *Hypertension*. 2004;44:776-782.

Assumptions in 1990s Driving Development of α -Blockers for BPH



Roehrborn CG, Schwinn DA. *J Urol*. 2004;171:1029-1035.

New Concepts in Drug Development of α -Blockers

α_1 -ARs and Human LUTS

Prostate	Spinal Cord	Detrusor	Vessels
α_{1A}	α_{1D}	α_{1D}	$\alpha_{1B} > \alpha_{1A}$

- ↓BOO
 - α_{1A} ARs in bladder neck and prostate
- ↓ LUTS
 - α_{1A} in bladder neck and prostate smooth muscle
 - α_{1D} in bladder
 - α_{1D} in sensory afferents and central nervous system
- ↓ Vascular interaction
 - α_{1B} in blood vessels

Roehrborn CG, Schwinn DA. *J Urol*. 2004;171:1029-1035.
Schwinn DA, Roehrborn CG. *Int J Urol*. 2008;15:193-199.

α -Adrenergic Selectivity of BPH Drugs

Study Type	Assessment
Pharmacologic	Receptor binding studies
Uroselectivity	Relative potency for inhibiting prostate vs vascular smooth muscle (in vitro studies)
Clinical	Efficacy vs adverse events in RCT

RCT, randomized, controlled trial.

Pharmacologic Selectivity Profiles of α -Blockers

α_1 -Blocker	α_1 -Receptor Selectivity
Doxazosin ¹	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Terazosin ¹	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Alfuzosin ¹	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Tamsulosin ^{1,2}	$\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$
Silodosin ³	$\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$

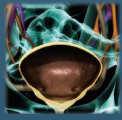
Results based on in vitro data

1. Schwinn DA, et al. *Mayo Clin Proc*. 2004;79:1423-1434.

2. Kenny BA, et al. *Br J Pharmacol*. 1996;118:871-878.

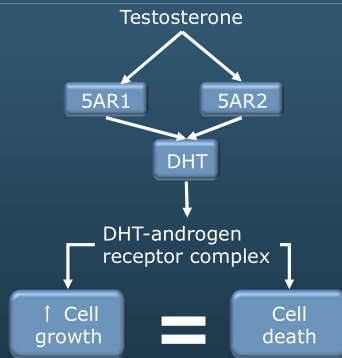
3. Akiyama K, et al. *J Pharm Exp Ther*. 1999;291:81-91.

Alpha-blocker Competitive Efficacy Review



5α-reductase inhibitors (5ARIs)

- For long-term use in men with enlarged prostates
- Exert an androgen effect on the prostate:
 - Finasteride: inhibits 5α-reductase type 2 only
 - Dutasteride: inhibits 5α-reductase types 1 and 2
- Act to reduce serum DHT concentrations
- Long half-life for dutasteride:
 - Finasteride: 6-8 hours
 - Dutasteride: 3-5 weeks



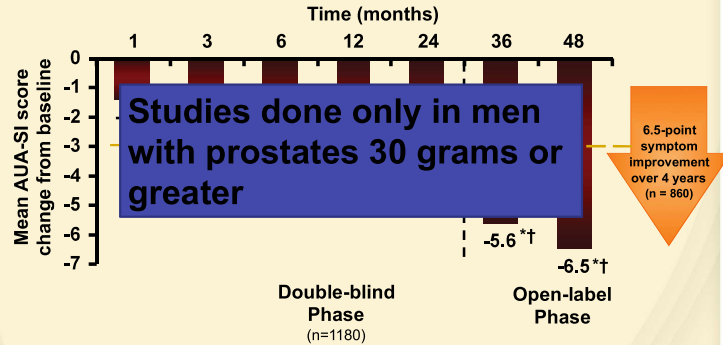
5AR1: 5α-reductase receptor 1;
5AR2: 5α-reductase receptor 2; DHT: dihydrotestosterone

Oelke M et al. Management of Male LUTS. European Association of Urology, 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

Dutasteride Reduces Symptoms



Pooled Results from Three Randomized, Placebo-controlled, 2-year Clinical Studies with 2-year Open-label Extension Phase with AVODART 0.5 mg daily



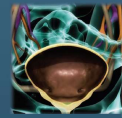
*P < 0.001 between treatment groups
†P < 0.001 vs month 24

Debruyne F, et al. Eur Urol. 2004;46:488-94.

A 5 Year Study Of 5 – Alpha Reductase Inhibitors In Men With Benign Prostatic Hyperplasia: Finasteride Has Equal Efficacy And Prostate Volume Reduction But Has Less Sexual Side Effects And Breast Enlargement Than Dutasteride

**Steven A. Kaplan, Doreen E. Chung,
Richard K. Lee, Scott Melamed,
Alexis E. Te**

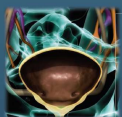
**Weill Cornell Medical College
Cornell University**



Finasteride Versus Dutasteride Results

Parameter	Finasteride (817)	Dutasteride (813)
Prostate Volume Reduction % at 12M	-26.7	-26.3
AUA SI @ 3M	-3.8	-3.6
AUA SI @ 12M	-5.5	-5.8
Qmax @ 12M	1.7 ml/sec	2.0 ml/sec

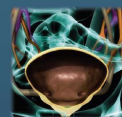
NO DIFFERENCE BETWEEN THE TWO GROUPS



Sexual Adverse Events

Parameter	Finasteride	Dutasteride
Change in IIEF	-2.4	-3.5
Decreased libido	1.4%	2.7%
Breast tenderness / enlargement	1.2%	3.5%

Significantly higher in dutasteride group (p < 0.01)

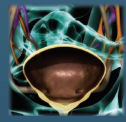


Efficacy 5ARIs

- Clinical effects are observed after a minimum treatment period of 6–12 months; therefore, long-term treatment necessary
- After 2–4 years of treatment, IPSS is reduced by ~15–30% and prostate size ↓ by 20–30%
- Symptom reduction (IPSS) is dependent on prostate size at treatment initiation
- In men with prostate sizes <30–40 ml efficacy is comparable with placebo

Oelke M et al. Management of Male LUTS. European Association of Urology, 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

IPSS: International Prostate Symptom Score

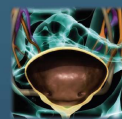
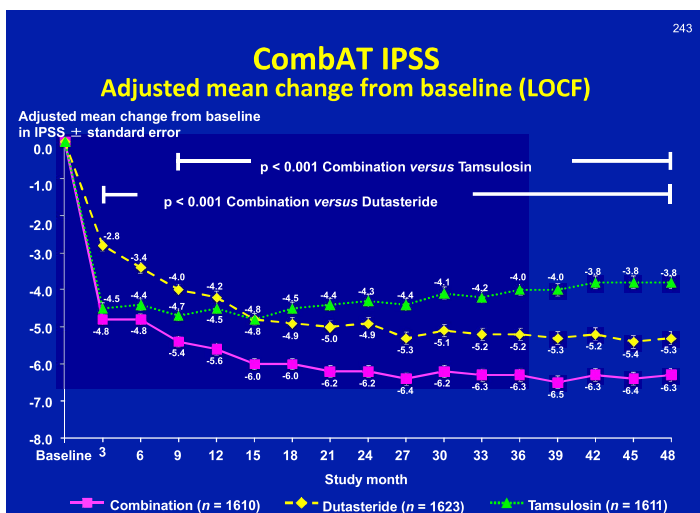
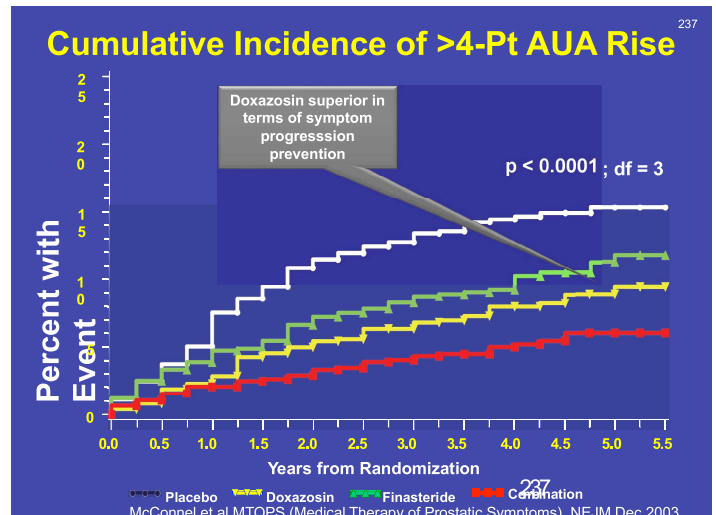
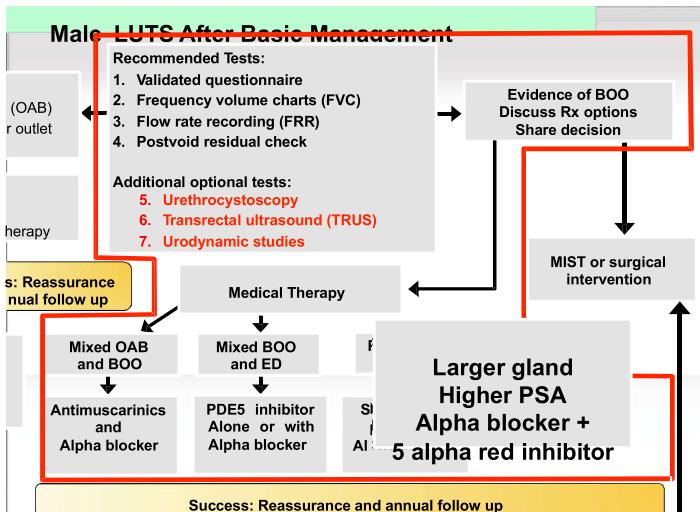
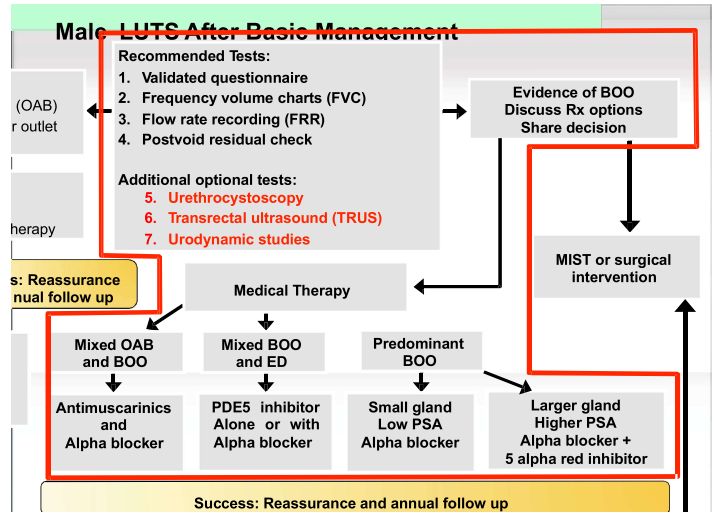


Efficacy 5ARIs

- Symptom (IPSS) reduction with 5-ARIs depends on:
 - Baseline PSA values $>4.4 \mu\text{g/l}$ → fastest symptom relief
 - Prostate volume $>58 \text{ ml}$ significant ↓ IPSS compared with smaller prostate volumes
- Reduce the risk of urinary retention or need-for-surgery

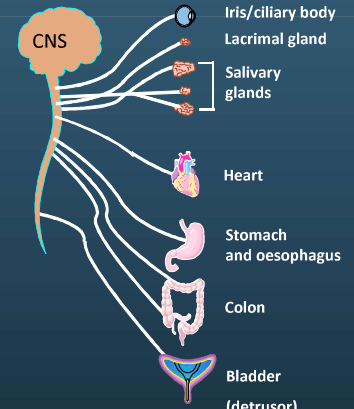
Oelke M et al. Management of Male LUTS. European Association of Urology, 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%202012.pdf]

IPSS: International Prostate Symptom Score



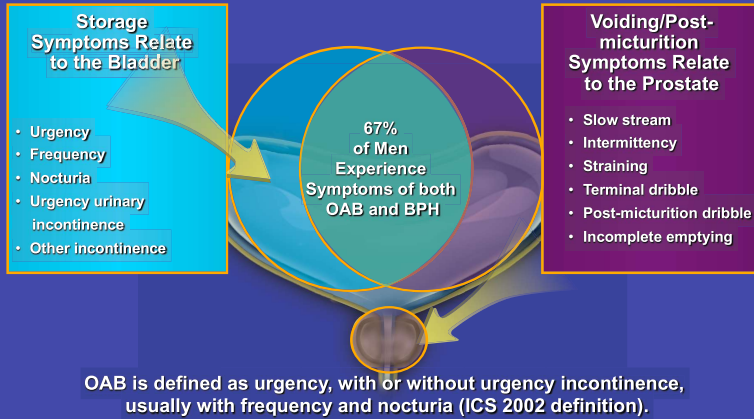
Muscarinic Receptor Antagonists

- Five muscarinic receptors have been described (M_1 - M_5)
- Expressed in the bladder, salivary glands, and synapses in the CNS
- M_2 and M_3 are most predominant in the bladder
- Only M_3 is involved in bladder contractility
- Inhibition of muscarinic receptors reduce smooth cell contractions of the bladder



Oelke M et al. Management of Male LUTS. European Association of Urology, 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%202012.pdf]

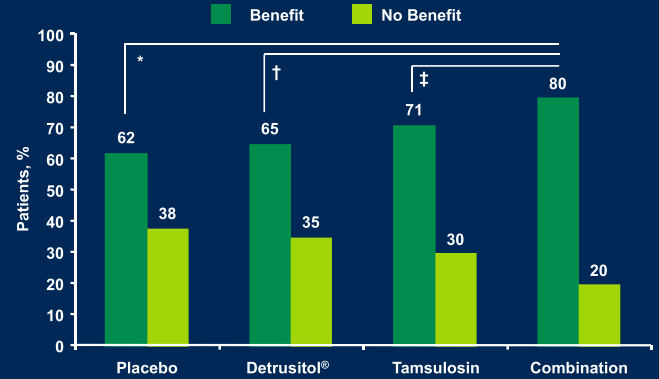
Most Men with LUTS Have Both Storage and Voiding/Post-micturition Symptoms



Irwin DE et al. *Eur Urol*. 2006;50:1306-1315.
Abrams P et al. *Urology*. 2003;61:37-49.

OAB = overactive bladder.

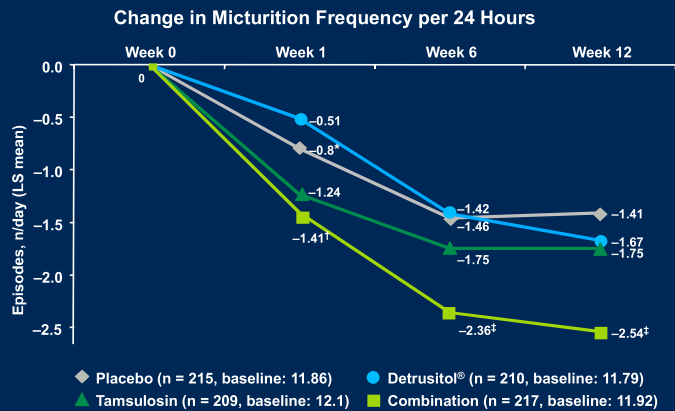
Treatment with Tolterodine plus Tamsulosin Resulted in Significant Treatment Benefit at Week 12



*P < .001 between-group comparisons.
†P = .001 between-group comparisons.
‡P < .05 between-group comparisons.

Kaplan SA et al. *JAMA*. 2006;296:2319-2328.

Treatment with Tolterodine plus Tamsulosin Significantly Reduced Frequency



*P < .05 vs placebo.
†P < .01 vs placebo.
‡P < .001 vs placebo.

Kaplan SA et al. *JAMA*. 2006;296:2319-2328.

Summary for Patients with Small Prostates and Low Levels of PSA (cont)

Prostate Size <29 ml / PSA <1.3 ng/ml

	Tolterodine	Tamsulosin	Combination
Frequency/24 hours	++/+++		+++/>

+++ P < .01;
++ P < .05;
+ .05 < P < .1; vs. placebo.

Summary for Patients with Large Prostates and High Levels of PSA (cont)

Prostate Size ≥29 ml / PSA ≥1.3 ng/ml

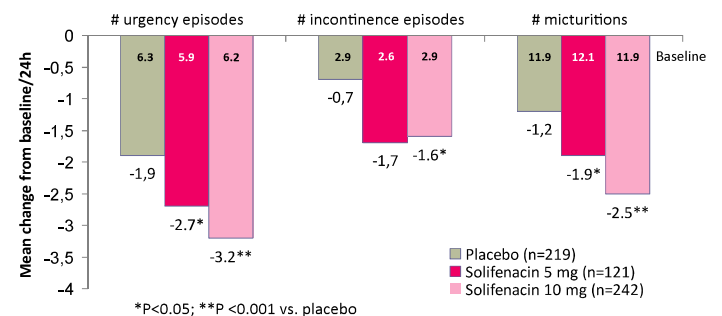
	Tolterodine	Tamsulosin	Combination
Frequency/24 hours			+++/>

+++ P < .01;
++ P < .05;
+ .05 < P < .1; vs. placebo.

Oelke®

Efficacy Antimuscarinics in Male LUTS

Meta-analysis: subgroup analysis of 582 men from 4 RCTs (phase III) evaluating the efficacy and safety of solifenacin (12 weeks) in male OAB patients (n=2,848)



*P < 0.05; **P < 0.001 vs. placebo

RCT: randomised controlled trial; OAB: overactive bladder

van Kerrebroeck P et al. *Eur Urol Suppl* 2005; 4: 61 (abstract 233)
Chapple CR et al. *Int J Clin Pract* 2006; 60: 959 - 966

Antimuscarinics ONLY in Male LUTS

Trials	Duration (weeks)	Treatment	Patients [N]	Voiding frequency [%]	Nocturia [%]	Urgency Incontinence [%]	IPSS [%]	LE
Kaplan et al. (2005)	25	Tolterodine 1 x 4mg/d (after α -blocker failure)	43	-35.7 *	-29.3 *	-	-35.5 *	2b
Roehrborn et al. (2006)	12	Placebo	86	-4	-	-40	-	1b
		Tolterodine 1 x 4mg/d	77	-12	-	-71 *	-	
Kaplan et al. (2006)	12	Placebo	374	-7.9	-17.6	-	-	1b
		Tolterodine 1 x 4mg/d	371	-10.8 *	-18.8	-	-	
Kaplan et al. (2006)	12	Placebo	215	-13.5	-23.9	-13	-44.9	1b
		Tolterodine 1 x 4mg/d	210	-16.5	-20.1	-85 *	-54	
Dmochowski et al. (2007)	12	Placebo	374	-5.6	-17.6	-	-	1b
		Tolterodine 1 x 4mg/d	371	-8.7	-18.8	-	-	
Höfner et al. (2007)	12	Tolterodine 1 x 4mg/d	741	-20 *	-42.9 *	-100	-37.9 *	2b
Herschorn et al. (2009)	12	Placebo	124	-10.2	-	59.3	-	1b
		Fesoterodine 1 x 4mg/d	111	-13.2 *	-	-84.5 *	-	
		Fesoterodine 1 x 8mg/d	109	-15.9 *	-	-100 *	-	

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

IPSS: International Prostate Symptom Score

PVR and Urinary Retention -Monotherapy Antimuscarinics-

TRIAL	Duration [weeks]	Treatment	Patients [N]	PVR [ml]	Retention N	Retention %
Kaplan et al. 2005	25	Tolterodine 1x4 mg/d	43	-22 *	0	0
Roehrborn et al. 2006	12	Placebo	86		0	0
		Tolterodine 1x4 mg/d	77		1	1.3
Kaplan et al. 2006	12	Placebo	374		2	0.5
		Tolterodine 1x4 mg/d	371		3	0.8
Kaplan et al. 2006	12	Placebo	215	-3.6	3	1.4
		Tolterodine 1x4 mg/d	210	+5.3	2	0.9
Dmochowski et al. 2007	12	Placebo	374		2	0.5
		Tolterodine 4 mg/d	371		4	1.1
Höfner et al. 2007	12	Tolterodine 1x4 mg/d	741	0	8	0.7
Chapple et al. 2009	12	Placebo	323	+1.1	6	1.9
		Tolterodine 1x4 mg/d	329	+14.3 *	6	1.8
Herschorn et al. 2010	12	Placebo	124		1	0.8
		Fesoterodine 1x4 mg/d	120	+9.6 **	1	0.8
		Fesoterodine 1x8 mg/d	114	+20.2 **	6	5.3

* P=0.023

**P=0.035

PVR: post-void residual

Adapted from Oelke M. UniMed Science. Hampel (Ed) 2009 pp84 - 97
Herschorn S et al. Urology 2010; 75; 1149 - 55

Other OAB Monotherapies

• Beta 3 adrenoreceptor agonist- Mirabegron

- No significant urodynamic changes in men
- Symptom improvement at 50 mg dosage

• PD5 Inhibitor Tadalafil

- Significant symptom improvement with improved erectile function
- No urodynamic impact/effect/changes
- Sounds like OAB Rx

1: Nitti V et al. J Urol. 2013 Oct;190(4):1320-7.
2: Chishti H, et al. Int Urol Nephrol. 2013 Feb;45(1):53-60.
3: Krawinkel W et al. Clin Ther. 2012 Oct;34(10):2144-60
4: Roehrborn CG et al. J Urol. 2013 Oct 25. S0022-5347(13)05757-1
5: Gacci M et. Res Rep Urol. 2013 Apr 6;5:99-111
6: Porst H, et al. J Sex Med. 2013 Aug;10(8):2044-52.

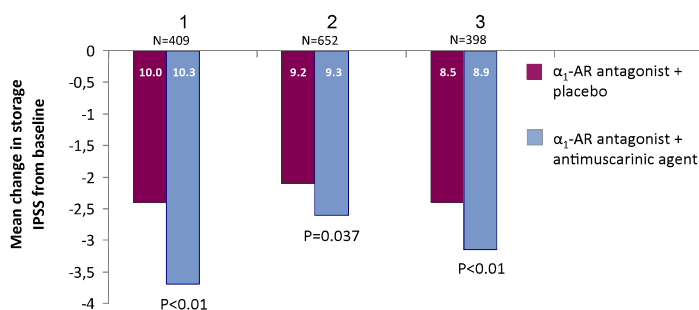
Combination Therapy

- α -blockers + muscarinic receptor antagonists:
 - Inhibit both α -adrenoceptors and muscarinic cholinoreceptors

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

Addition of an antimuscarinic to an α_1 -blocker improves persistent storage symptoms

12-week, double-blind RCTs in men ≥ 40 or 45 yr with OAB symptoms after ≥ 4 w on α_1 -AR antagonist
 $Q_{max} \geq 4$ or 5 ml/s; PVR ≤ 200 ml (type of active agents differs between studies)



¹ MacDiarmid SA et al. Mayo Clin Proc 2008; 83: 1002 - 1010

² Chapple C et al. Eur Urol 2009; 56: 534 - 543

³ Kaplan SA et al. J Urol 2009; 182: 2825 - 2830

IPSS: International Prostate Symptom Score; RCT: randomised controlled trial;
OAB: overactive bladder; PVR: post-void residual

α_1 -blocker + Antimuscarinic

Trials	Duration (weeks)	Treatment (daily dose)	Patients [N]	Voiding frequency [%]	Nocturia [%]	IPSS [%]	LE
Saito et al. (1999)	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5		1b
		Tamsulosin + propiverine 1 x 20 mg/d	75	-44.7	-44.4 *		
Lee et al. (2005)	8	Doxazosin 1 x 4 mg/d	67	-11.8	-37.5	-54.9	1b
		Doxazosin + propiverine 1 x 20 mg/d	131	-27.5 *	-46.7	-50.7	
Kaplan et al. (2006)	12	Placebo	215	-13.5	-23.9	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-54	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9 *	
		Tolterodine + tamsulosin	217	-27.1 *	-39.9 *	-66.4 *	
MacDiarmid et al. (2008)	12	Tamsulosin 1 x 0.4 mg/d	209	-	-	-34.9	1b
		Tamsulosin + oxybutynin 1 x 10 mg/d	209	-	-	-51.9 *	
Kaplan et al. (2005)	25	Tolterodine 1 x 4 mg/d	43	-35.7 *	-29.3 *	-35.3 *	2b
Yang et al. (2007)	6	Tolterodine 2 x 2 mg/d	33	-	-	-35.7 *	2b
Kaplan et al. (2009)	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2 *	-	-29	1b
		Tamsulosin 1 x 0.4 mg/d + solifenacin 5 mg/d	202	-9.1 *	-	-31.8	

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

IPSS: International Prostate Symptom Score

The Health Improvement Network (THIN) Database: Focused Safety Study of Acute Urinary Retention (AUR) in Men

Luis Alberto García-Rodríguez, Elisa Martín-Merino, Elvira Luján Massó-González, Claus G. Roehrborn

This study was funded by Pfizer Inc

Relative Risk of Acute Urinary Retention by Antimuscarinic Timing of Use, Duration, and Daily Dose*

	Number (%) of Patients		RR†	95% CI
	Cases (n=1844)	Controls (n=10,000)		
Use				
Non-use	1706 (93)	9727 (97)	1	
Timing of use				
Current use	94 (5)	154 (2)	2.9	2.2–3.7
Recent use	15 (<1)	39 (<1)	1.7	0.9–3.1
Past use	29 (2)	80 (<1)	1.6	1.0–2.5
Duration: Current use				
≤30 days	38 (40)	22 (14)	8.3	4.8–14.2
31 days–1 year	28 (30)	60 (39)	2.0	1.2–3.1
>1 year	28 (30)	72 (47)	2.0	1.3–3.1
Daily dose/indication: Current use				
Low/medium dose	84 (89)	138 (90)	2.8	2.1–3.8
High dose urogenital	10 (11)	16 (10)	3.0	1.3–6.8

*Percentages for timing of use are based on overall study cohort (1844 cases; 10,000 controls); percentages for duration and daily dose are based on the number of patients currently using antimuscarinics (94 cases, 154 controls).

†Relative risk estimates were adjusted for age, calendar year, general practitioner visits, and oral antimuscarinic use.

PVR and Urinary Retention -Monotherapy Antimuscarinics-

TRIAL	Duration [weeks]	Treatment	Patients [N]	PVR [ml]	Retention N %
Kaplan et al. 2005	25	Tolterodine 1x4 mg/d	43	- 22*	0 0
Roehrborn et al. 2006	12	Placebo	86		0 0
		Tolterodine 1x4 mg/d	77		1 1.3
Kaplan et al. 2006	12	Placebo	374		2 0.5
		Tolterodine 1x4 mg/d	371		3 0.8
Kaplan et al. 2006	12	Placebo	215	- 3.6	3 1.4
		Tolterodine 1x4 mg/d	210	+ 5.3	2 0.9
Dmochowski et al. 2007	12	Placebo	374		2 0.5
		Tolterodine 4 mg/d	371		4 1.1
Höfner et al. 2007	12	Tolterodine 1x4 mg/d	741	0	8 0.7
Chapple et al. 2009	12	Placebo	323	+ 1.1	6 1.9
		Tolterodine 1x4 mg/d	329	+ 14.3 *	6 1.8
Herschorn et al. 2010	12	Placebo	124		1 0.8
		Fesoterodine 1x4 mg/d	120	+ 9.6**	1 0.8
		Fesoterodine 1x8 mg/d	114	+ 20.2**	6 5.3

* P=0.023

**P=0.035

Adapted from Oelke M. UniMed Science. Hampel (Ed) 2009 pp84 - 97
Herschorn S et al. Urology 2010; 75; 1149 - 55

PVR: post-void residual

EAU Recommendations

EAU
European
Association
of Urology

Antimuscarinic monotherapy

Recommendations	LE	GR
Muscarinic receptor antagonists might be considered in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms	1b	B
Caution is advised in men with bladder outlet obstruction	4	C

Antimuscarinic + α_1 -blocker combination therapy

Recommendations	LE	GR
Combination treatment with a muscarinic receptor antagonist and an α_1 -blocker might be considered in patients with moderate-to-severe LUTS if symptom relief has been insufficient with monotherapy with either drug	1b	B
Combination treatment should be used cautiously in men suspected of having bladder outlet obstruction	2b	B

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

Options/Recommendations: Anticholinergics

Option:

Anticholinergic agents are appropriate alternatives for the management of LUTS/BPH in men without an elevated PVR and when LUTS are predominantly irritative.

Recommendations:

Prior to initiation of anticholinergic Rx, baseline PVR should be assessed.

Anticholinergics should be used with caution in men with PVR>250-300 mL.

Based on Panel consensus

Mirabegron Primary Results Published in European Urology

ARTICLE IN PRESS

Efficiency and Tolerability of Mirabegron, a β_2 -Adrenoceptor Agonist, in Patients with Overactive Bladder Results from a Randomized European-Australian Phase 3 Trial

Uk Khullar*, Geoff Rowland†, Javier C. Aguirre, Javier Centeno*, April Hsu*, Ian Millar, Peter Rabinovich, Stuart Reicher†, Peter Roehrborn†, Tim Thompson†, Hanser Wessing†, Christopher Chapple†

Abstract

Objective: To evaluate the efficacy and tolerability of mirabegron, a β_2 -adrenoceptor agonist, in patients with overactive bladder (OAB) symptoms. The primary endpoint was the proportion of patients achieving a ≥50% reduction in the number of voids per day (NVD) compared with placebo.

Design: A randomized, double-blind, placebo-controlled, phase 3 trial. Patients were randomized to receive mirabegron (50 mg twice daily) or placebo for 12 weeks. The primary endpoint was the proportion of patients achieving a ≥50% reduction in NVD compared with placebo. Secondary endpoints included the proportion of patients achieving a ≥50% reduction in the number of urgency episodes per day (NEPD), the proportion of patients achieving a ≥50% reduction in the number of nocturnal voids (NV), and the proportion of patients achieving a ≥50% reduction in the number of incontinence episodes per day (NIEPD).

Results: A total of 1000 patients were randomized to receive mirabegron (500) or placebo (500). The primary endpoint was achieved in 75% of patients in the mirabegron group compared with 50% in the placebo group. Secondary endpoints were also significantly improved in the mirabegron group compared with the placebo group.

Conclusion: Mirabegron (50 mg twice daily) is an effective and well-tolerated treatment for OAB symptoms. It significantly improves NVD, NEPD, NV, and NIEPD compared with placebo.

Keywords: Mirabegron, β_2 -adrenoceptor agonist, overactive bladder, NVD, NEPD, NV, NIEPD.

Introduction

Overactive bladder (OAB) is a common condition that affects millions of people worldwide. It is characterized by a feeling of urgency, frequency, and nocturia, which can significantly impact quality of life. Current treatments for OAB include anticholinergics and α_1 -blockers. However, these treatments can have side effects such as dry mouth, constipation, and dizziness. Mirabegron, a β_2 -adrenoceptor agonist, is a new class of drug that has been shown to be effective in treating OAB symptoms without the side effects of anticholinergics and α_1 -blockers. This study was designed to evaluate the efficacy and tolerability of mirabegron in patients with OAB symptoms.

Methods

This was a randomized, double-blind, placebo-controlled, phase 3 trial. Patients were randomized to receive mirabegron (50 mg twice daily) or placebo for 12 weeks. The primary endpoint was the proportion of patients achieving a ≥50% reduction in NVD compared with placebo. Secondary endpoints included the proportion of patients achieving a ≥50% reduction in the number of urgency episodes per day (NEPD), the proportion of patients achieving a ≥50% reduction in the number of nocturnal voids (NV), and the proportion of patients achieving a ≥50% reduction in the number of incontinence episodes per day (NIEPD).

Results

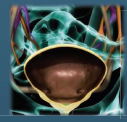
A total of 1000 patients were randomized to receive mirabegron (500) or placebo (500). The primary endpoint was achieved in 75% of patients in the mirabegron group compared with 50% in the placebo group. Secondary endpoints were also significantly improved in the mirabegron group compared with the placebo group.

Conclusion

Mirabegron (50 mg twice daily) is an effective and well-tolerated treatment for OAB symptoms. It significantly improves NVD, NEPD, NV, and NIEPD compared with placebo.

Keywords

Mirabegron, β_2 -adrenoceptor agonist, overactive bladder, NVD, NEPD, NV, NIEPD.



Mirabegron key studies Completed

Completed Study	Description	Primary Endpoints
SYMPHONY	Evaluate the Efficacy, Safety and Tolerability of Mirabegron and Solifenacin Alone and in Combination for the Treatment of Overactive Bladder	- Change from baseline to EOT in mean number of micturitions/ 24 hours - Change from baseline to EOT in mean number of incontinence episodes/24 hours
BEYOND	Evaluate the efficacy and safety of mirabegron compared to solifenacin in patients with OAB who are previously treated with another medicine but were not satisfied with that treatment	Change from baseline in the mean number of micturitions per 24 hours, based on a 3-day micturition diary at Weeks 4, 8, and 12

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Plant Extracts

Table 8: Trials with plant extracts in patients with BPH-LUTS (selection; in alphabetical order)

Trials	Duration (weeks)	Treatment	Patients (n)	Change in symptoms (IPSS) †	Change in Q _{max} [mL/s] ‡	PVR [mL] §	LE ¶
Bach (2000) (8)	52	placebo Cucurbita pepo (Prosta Plus™ forte)	243 233	-5.5 -5.7 #	n.s. n.s.	n.s. n.s.	1b
Gengen et al. (1999) (8)	34	placebo Hypoxis rooperi (Hypoxis™)	100 100	-3.5 -7.4 *	-1.1 +5.2 *	-14.9 -35.4 *	1b
Köppel et al. (1997) (8)	26	placebo Hypoxis rooperi (Hypoxis™)	89 88	-2.8 -5.2 *	+4.3 +8.8 *	-4.1 -37.5 *	1b
Witt et al. (2000) (7)	4-26	placebo Hypoxis rooperi	475	-4.9 #	-3.9 #	-28.6 #	1a
Witt et al. (2002) (10)	4-16	placebo Pygeum africanum (p-sitosterol)	1562	RR 2.07 #	+2.5 #	-13.2 #	1a
Witt et al. (2000) (11)	12-24	placebo Saclea caraeale (Cemillon™)	444	RR 2.4 #	-1.6	-14.4	1a
Witt et al. (2002) (18)	4-48	placebo Sarcocolla repens/ Sabal serrulata	3139	-1.41 #	+1.86 #	-23 #	1a
Shen et al. (2006) (19)	83	placebo Sarcocolla repens	113 112	0.7 -0.7	0.04 -0.42	-14 10	1b
Garraro et al. (1996) (20)	26	flavonoids Sarcocolla repens (Permixon™)	945 953	-6.2 -5.8	+3.2* +2.7	-	1b
Debruyne et al. (2002) (21)	52	tamsulosin Sarcocolla repens (Permixon™)	354 350	-4.4 -4.4	+1.9 +1.8	-	1b
Schneider & Robben (2004) (14)	52	placebo Urtica dioica (Bacolon Uno™)	122 124	-4.7 -5.7 *	+2.9 +3.0	-4 -5	1b
Safarinejad (2005) (15)	26	placebo Urtica dioica	316 305	-1.5 -4.3 *	+3.4 +3.0	0 -5	1b
Lopatin et al. (2005) (16)	24	placebo Sabal serrulata + Urtica dioica (Prostatgut™ forte)	127	-6.1	+1.9	-	1b
Schuland & Albrecht (1997) (17)	48	flavonoids Sabal serrulata + Urtica dioica (Prostatgut™ forte)	244 245	-5.6 -4.8	+2.8 +2.8	-17.1 -19.2	1b



Secale cereale



Urtica radix



Sabal serrulata



Cucurbita pepo

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Plant Extracts

- Phytherapeutic agents are a heterogeneous group of plant extracts used to improve LUTS/BPH
- Problematic because of different concentrations of active ingredient(s) in different brands of the same phytherapeutic agent
- Meta-analyses of extracts of the same plant are not justified and results of these analyses have to be interpreted with caution
- Further studies are necessary to adequately judge plant extracts

3.4.6 Recommendations

The guidelines committee is unable to make specific recommendations about phytherapy of male LUTS because of the heterogeneity of the products and the methodological problems associated with meta-analyses.

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gis/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

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‘Emerging’ Therapies

- Phosphodiesterase 5 (PDE5) inhibitors
 - Alone and in combination with α -blockers
- Available drugs include
 - Sildenafil
 - Tadalafil
 - Vardenafil

Table 13: PDE5 inhibitors licensed in Europe for treating erectile dysfunction; key pharmacokinetic properties and doses used in clinical trials

Drugs	t _{max} (hours)	t _{1/2} (hours)	Daily doses in clinical trials of patients with male LUTS
Sildenafil	1* (0.5-2)	3-5	1 x 25-100 mg
Tadalafil	2 (0.5-12)	17.5	1 x 2.5-20 mg
Vardenafil	1* (0.5-2)	4-5	2 x 10 mg

- No PDE5 inhibitor is indicated for use in LUTS and use is still off-label
BUT tadalafil has been approved in Europe since October 2012

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gis/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

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Efficacy PDE5 inhibitors

Table 14: Efficacy of PDE5 inhibitors in adult men with LUTS who participated in clinical trials with EBM Level 1b

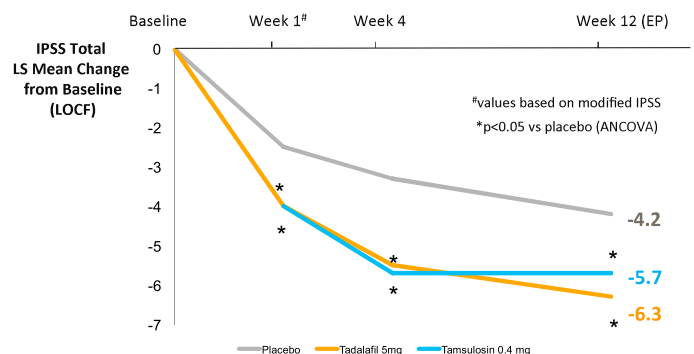
Trials	Duration (weeks)	Treatment	Patients	IPSS	Q _{max} [mL/s]	PVR [mL]	LE
McVary et al. 2007 (9) 2	12	Placebo Sildenafil 1 x 50-100 mg/day or 1 x 50-100 mg before sexual intercourse	180 189	-1.93 -4.32 *	+5.16 +2.32	-	1b
Kaplan et al. 2007 (32)	12	Placebo Tadalafil 1 x 10 mg/day Tadalafil 1 x 20 mg/day	20 41 21	-2.7 -5.15 (94%) -4.3	+1.1 +1.8 +3.2	-23.1 -10 -21.7	1b
McVary et al. 2007 (10)	12	Placebo Tadalafil 1 x 5-20 mg/day	143 138	-1.7 -3.8	+0.8 +0.5	-0.6 +1.4	1b
Rosenbom et al. 2008 (11)	12	Placebo Tadalafil 1 x 2.5 mg/day Tadalafil 1 x 5 mg/day Tadalafil 1 x 10 mg/day Tadalafil 1 x 20 mg/day	212 209 212 216 209	-0.9 -3.7 -3.22 (94%) -3.8 (95.2%) -5.2	+1.2 +1.4 +1.6 +2.0	+4.91 +12.1 +6.8 -4	1b
Bechara et al. 2009 (12)	6	Tamsulosin 1 x 0.4 mg/day Tamsulosin 1 x 0.4 mg/day + tadalafil 1 x 20 mg/day	16 15	-6.7 -9.3	+2.1 +3.3	-32.2 -38.7	1b
Lipschultz et al. 2009 (13) 2	12	Placebo Tadalafil 1 x 10 mg/day Tadalafil 1 x 20 mg/day	22 21 23	-2.9 -4.7 -4.3	+1.7 +1.7 +3.1	-	1b
Pugh et al. 2009 (14)	12	Placebo Tadalafil 1 x 2.5 mg/day Tadalafil 1 x 5 mg/day Tadalafil 1 x 10 mg/day Tadalafil 1 x 20 mg/day	115 117 120 118	-2.1 -4.2 -4.7 -5.1	+1.8 +1.6 +1.3 +1.8	-6.8 -5.8 -5.8 -5.8	1b
Staff et al. 2008 (15)	8	Placebo Vardenafil 2 x 10 mg	108 108	-2.6 -5.8	+1.0 +1.8	+1.82 -1.5	1b

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gis/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]

IPSS: International Prostate Symptom Score;
Q_{max}: maximum urinary flow; QoL: quality of life

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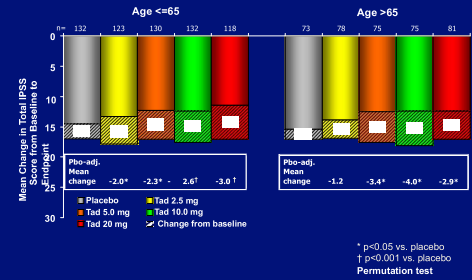
Both Tadalafil and Tamsulosin Improve IPSS ...



Oelke M et al. Eur Urol 2012; 61: 917 - 25

PDE – 5 Inhibitors Do Not Improve Q_{max}: A Contrarian View

IPSS Total Score Change stratified by Age



Review

Relationship Between ED and LUTS and the Role of PDE5 Inhibitors

Study	Agent Dose Duration	N (n)	Inclusion	Placebo Run-in	IPSS Δ: PDE-5 vs Placebo (P-value)	Other Findings
McVary et al	Sildenafil 50–100 mg qday 12 wk	369 (189)	Age ≥45, history of ED, <25 IIEF (EF domain), IPSS ≥12	No	6.3 vs 1.9 (P<0.0001)	No change in Q _{max}
Stef et al	Vardenafil 10 mg bid 8 wk	222 (109)	Age 45–64, IPSS ≥12, no history of ED required	No	5.9 vs 3.6 (P=0.0013)	No change in Q _{max}
McVary et al	Tadalafil 5 mg → 20 mg qday 4-wk run-in + 12 wk (6 → 6)	281 (138)	Age ≥45, IPSS ≥12 from BPH for 6 mo, no history of ED required	Yes	5 mg 2.8 vs 1.2 (P=0.003) 20 mg 3.8 vs 1.7 (P<0.001) 7.1 vs 4.5 (P<0.001); includes run-in	No change in Q _{max}

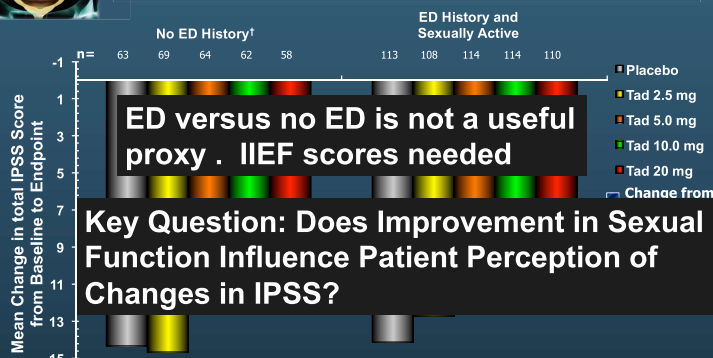
BI, BPH Impact Index; GAQ, Global Assessment Question; PVR, postvoid residual; Q_{max}, maximum flow rate; QoL, quality of life; Kähler TS, McVary KT. Eur Urol. 2009;55(1):38–48.

Summary of Key Urodynamic Outcomes

Measure	Difference of Change* (tadalafil – placebo)		
	Mean	SE	(P-value)
Free-flow Assessments:			
Peak Flow Rate	-0.60	1.48	0.685
Postvoid Residual Volume by Cath	-13.02	14.67	0.376
Total Bladder Capacity	3.53	31.95	0.912
Bladder Voiding Efficiency	2.73	3.16	0.389
Pressure-flow Assessments: PdetQ_{max}			
Peak Flow Rate	-2.18	2.21	0.325
	-0.12	0.45	0.785
Bladder Outlet Obstruction Index	-1.93	2.54	0.448

*Mean difference of change, SE, and p-value for difference between treatment group and placebo are from ANOVA based upon the type II sum of squares approach, stratified by the 6 randomization strata (bladder outlet obstruction class by LUTS severity). J Urol 2010 Mar;183(3):1092-7

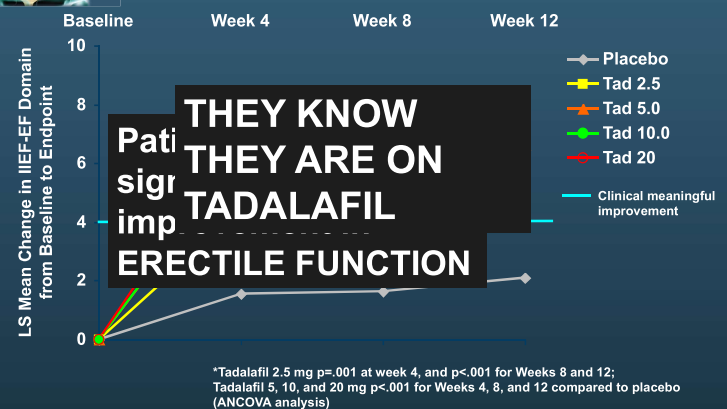
IPSS Changes Stratified by ED History



* p<.05 compared to placebo (ANCOVA analysis)

Roehrborn et al J Urol 2008 Oct;180(4):1228–34

IIEF-EF Domain Change from Baseline to Endpoint after 4, 8, and 12 Weeks



Primary and Secondary Outcomes

Men Who Claim They Have No Erectile Dysfunction Have Significant Improvement from a PDE – 5

Sexual Relationship domain

Timepoint	Placebo (n=137)	Sildenafil (n=129)
Baseline	49.5	48.3
Week 4	6.1±2.4	23.2±2.4

Therefore, Even Normal Men Were Unblinded: THEY KNEW THEY WERE TAKING TADALFIL

*N=138 in the placebo group for the IIEF-EF domain.

†P=0.0001 vs. placebo.

‡P=0.0112 vs. placebo.

§EDITS data are end of treatment scores and included 138 men in the placebo group and 128 men in the sildenafil group.

Shabsigh R. et al. Urology. 2010 Aug;76(2):373-9.

72

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Efficacy and Safety of the Coadministration of Tadalafil Once Daily with Finasteride for 6 Months in Men with Lower Urinary Tract Symptoms and Prostatic Enlargement Secondary to Benign Prostatic Hyperplasia

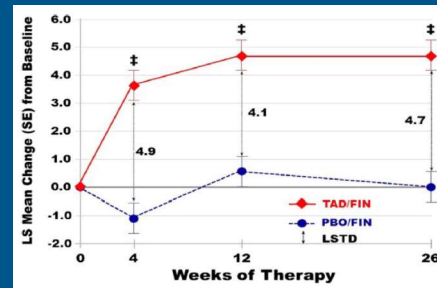


Figure 4. Time course of LS mean change (SE) from baseline in IIEF EF score in men who were sexually active with ED at baseline (201 for PBO/FIN, 204 for TAD/FIN). Double dagger indicates $p < 0.001$.

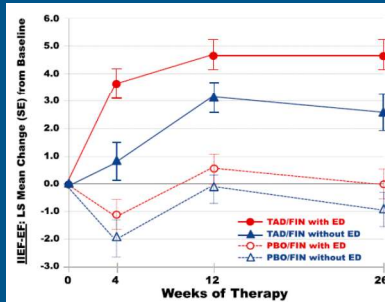
Casabe, Roehrborn et al. Vol. 191, 727-733, March 2014

3/11/2017

Urology Department

UTSouthwestern
Medical Center

Sexual Function in Men with Lower Urinary Tract Symptoms and Prostatic Enlargement Secondary to Benign Prostatic Hyperplasia: Results of a 6-Month, Randomized, Double-Blind, Placebo-Controlled Study of Tadalafil Coadministered with Finasteride



Time course of least squares mean changes (with standard errors) from baseline in International Index of Erectile Function-Erectile Function domain (IIEF-EF) scores in sexually active men who did not have erectile dysfunction (ED) at baseline (N = 102 for tadalafil [TAD]/finasteride [FIN]; N = 104 for placebo [PBO]/FIN) compared with the results obtained for sexually active men with ED (N = 203 for TAD/FIN; N = 201 for PBO/FIN). TAD/FIN resulted in significant improvements in IIEF-EF domain scores (compared with PBO/FIN) at all three postbaseline timepoints among men with baseline ED ($P \leq 0.001$ for all) and among men who did not have baseline ED ($P < 0.05$ at all three postbaseline timepoints). LS = least squares; PBO/FIN = placebo with finasteride 5 mg once daily; SE = standard error; TAD/FIN = tadalafil 5 mg with finasteride 5 mg once daily.

Glina, Roehrborn et al J Sex Med 2015;12:129-138

Urology Department

UTSouthwestern
Medical Center

Sexual Function in Men with Lower Urinary Tract Symptoms and Prostatic Enlargement Secondary to Benign Prostatic Hyperplasia: Results of a 6-Month, Randomized, Double-Blind, Placebo-Controlled Study of Tadalafil Coadministered with Finasteride

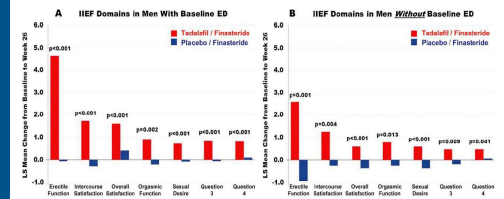
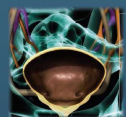


Figure 3. Comparison of least squares mean changes from baseline to week 26 in IIEF subdomain scores for: (A) men who were sexually active and had erectile dysfunction (ED) at baseline (N = 203 for tadalafil [TAD]/finasteride [FIN]; N = 201 for placebo [PBO]/FIN); (B) men who were sexually active but did not have ED at baseline (N = 102 for TAD/FIN; N = 104 for PBO/FIN). IIEF = International Index of Erectile Function; LS = least squares.

TAD/FIN reevaluated in 11m

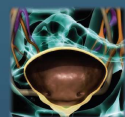
Glina, Roehrborn et al J Sex Med 2015;12:129-138

75



PDE – 5 Inhibitors / LUTS Thoughts

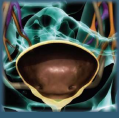
- Mechanism of Action is well defined for α_1 -Adrenoceptor Antagonists
- No widely accepted mechanism of action for PDE – 5
 - Lots of theories
 - ? bladder



Which Agent?

Lots of factors

- Specific findings assessed during evaluation
- Treatment preferences of the individual patient
- Ability of the treatment modality to change assessed findings

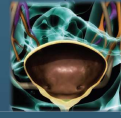


Which Agent?

What do patient and prescriber consider relevant?

- speed of onset
- efficacy
- side effects
- quality of life
- disease progression

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012
[www.uroweb.org/gls/pdf/12_Male_LUTS_LR%20May%209th%202012.pdf]



Men's Health

- Urologists have been playing small ball
- Need to expand
 - Advocacy
 - Preventive care
 - Holistic
- Expand beyond prostate and sexual function

AUA Guidelines 2018: Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia – Surgical Therapies

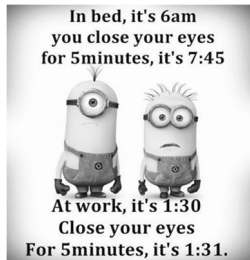
Lori Lerner, MD
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Boston University School of Medicine

Disclosures

- Lumenis, Inc – Preceptor, prior consultant
- Boston Scientific – Preceptor, prior consultant

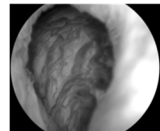
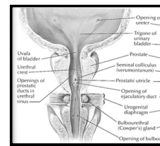
All activities other than precepting HoLEP have been suspended during the duration of the Guidelines development/process

Learning Objective



Be able to differentiate between non medical therapeutic options for BPH and understand which procedures are appropriate for which patients.

Background



- Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.
- While several hypotheses exist, BPH is likely the result of a multifactorial process, the exact etiology of which is unknown.
- The prevalence and the severity of lower urinary tract symptoms (LUTS) in the aging male can be progressive and is an important diagnosis in the healthcare of patients and the welfare of society.

Purpose

- The purpose of this revised guideline is to provide a useful reference on the effective evidence-based surgical management of male LUTS secondary to BPH (LUTS/BPH).
- The strategies recommended in this document were derived from evidence-base processes and a multi-disciplinary panel (general urology, surgical urology, primary care, patient advocacy).
- The most effective approach for a particular patient is best determined by shared decision making by the individual clinician and patient in the context of that patient's history, values, and goals for treatment.



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Methodology

- All modalities compared to TURP
- Whether or not this was best option is debatable, but guidelines should be taken within this context





Evaluation and Preoperative Testing

AUA-Symptom Index

1. Clinicians should take a medical history and utilize the AUA-Symptom Index (AUA-SI) and urinalysis in the initial evaluation of patients presenting with bothersome LUTS possibly attributed to BPH; select patients may also require post-void residual (PVR), uroflowmetry, or pressure flow studies. (Clinical Principle)

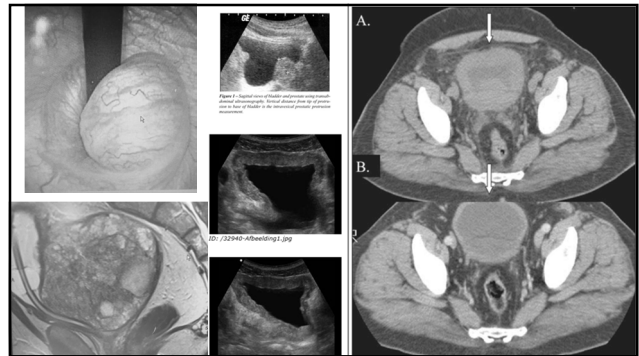
- AUA-SI is a validated self-administered questionnaire, can provide information regarding the symptom burden
- Urinalysis can help to rule out other causes of LUTS
- Shared decision making approach should be used to guide the need for further evaluation and possible treatment



Prostate Imaging

2. Clinicians should consider assessment of prostate size and shape via abdominal or transrectal ultrasound, or cystoscopy, or by preexisting cross-sectional imaging (i.e. magnetic resonance imaging [MRI]/ computed tomography [CT]) prior to surgical intervention for LUTS attributed to BPH. (Clinical Principle)

- Prostate size and morphology is important in the decision making process
 - eg, Intravesical lobe and ball-valving middle lobe predict poor outcomes
- DRE and PSA are rough indicators of prostate size
 - Reasonable to recommend imaging
 - ~ Abdominal or transrectal ultrasonography or cystoscopy
 - ~ Cross-sectional imaging using CT or MRI



PVR Assessment

3. Clinicians should perform a PVR assessment prior to surgical intervention for LUTS attributed to BPH. (Clinical Principle)



- Multiple organizations include PVR measurement as part of the basic evaluation of LUTS
- Rising PVR can indicate medication failure and need for surgical intervention
- PVR does not seem to be a strong predictor of acute urinary retention
 - Clinically useful test that may drive management choices

Uroflowmetry

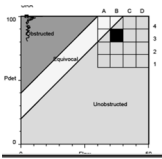
4. Clinicians should consider uroflowmetry prior to surgical intervention for LUTS attributed to BPH. (Clinical Principle)

- Generally accepted minimum threshold voided volume for adequate interpretation is 150 cc
 - Flow rate, shape of curve of voiding, duration
- Underactive detrusor function
 - Bladder diverticulum



Pressure Flow Studies

5. Clinicians should consider pressure flow studies prior to surgical intervention for LUTS attributed to BPH when diagnostic uncertainty exists. (Expert Opinion)



- “Most complete” means to determine the presence of bladder outlet obstruction (BOO) with testing
- Likelihood of obstruction is greatly increased in patients with a $Q_{max} < 10 \text{ mL/s}$
- Large volume PVR weakly correlated with obstruction
- OAB symptoms and incontinence can be sequelae of obstruction or secondary to non-obstructive etiologies
 - Surgery in these individuals may not lead to meaningful improvement

Surgical Therapy



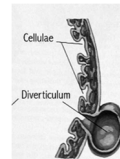
Surgery

6. Surgery is recommended for patients who have renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross hematuria due to BPH, and/or with LUTS attributed to BPH refractory to and/or unwilling to use other therapies. (Clinical Principle)

- Rates of surgical interventions dropping
 - Those patients receiving surgery are generally older and have more medical comorbidities
 - Surgery is mainstay in men with refractory urinary retention thought secondary to BPH

Bladder Diverticulum

7. Clinicians should not perform surgery solely for the presence of an asymptomatic bladder diverticulum; however, evaluation for the presence of BOO should be considered. (Clinical Principle)



- Indications for surgical intervention: recurrent UTI, recurrent bladder stones, progressive bladder dysfunction, and renal insufficiency secondary to progressive bladder dysfunction
- Prior to surgery for bladder diverticulum, clinicians should perform assessment for BOO and treat as clinically indicated

Transurethral Resection of the Prostate (TURP)

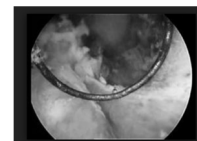
8. TURP should be offered as a treatment option for men with LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)

- TURP is gold standard
- TURP helps to reduce urinary symptoms associated with BPH:
 - Frequent/urgent need to urinate
 - Difficulty initiating urination
 - Prolonged urination
 - Nocturia
 - Non-continuous urination
 - Feeling of incomplete bladder emptying
 - UTIs

Approach to TURP

9. Clinicians may use a monopolar or bipolar approach to TURP, depending on their expertise with these techniques. (Expert Opinion)

- No significant differences in efficacy or effectiveness between monopolar and bipolar approaches
- Safety differences:
 - Bipolar TURP reduces
 - ~ Incidence of TUR syndrome
 - ~ Catheterization time
 - ~ Length of stay
 - ~ Dilutional hyponatremia



Simple Prostatectomy

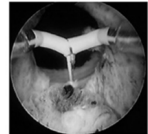
10. Clinicians should consider open, laparoscopic or robotic assisted prostatectomy, depending on their expertise with these techniques, for patients with large prostates. (Moderate Recommendation; Evidence Level: Grade C)

- Complications increase with increasing resection time and increasing resected tissue volume following monopolar TURP
 - Bipolar TURP extends safe duration of TURP and use for larger glands
- Open simple prostatectomy (OSP) compared to TURP
 - OSP: Greater maximum flow rate at 12 months
 - Lower reoperation
 - No difference in blood transfusion needs

Transurethral Incision of the Prostate (TUIP)

11. TUIP should be offered as an option for patients with prostates ≤30g for the surgical treatment of LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)

- Used to treat small prostates (usually defined as ≤30g)
- TUIP has lower rate of retrograde ejaculation, need for blood transfusion, compared to TURP
- Procedure can be performed with “hot knife” or laser
- ED in 8% with TUIP, 20% with TURP¹



1. Abd-El Kader O, et al. Afr J Urol 2012; 18: 29.

Transurethral Vaporization of the Prostate (TUVP)

12. Bipolar TUVP may be offered to patients for the treatment of LUTS attributed to BPH. (Conditional Recommendation; Evidence Level: Grade B)

- Multiple electrode types
- Metanalysis outcomes were similar in both groups
 - Long-term response to treatment based on varying definitions using the International Prostate Symptom Score (IPSS)
 - Mean change in IPSS through 7 years
 - Need for reoperation
 - Urinary incontinence
 - However, need for blood transfusion was lower for TUVP compared with TURP



Photoselective Vaporization of the Prostate (PVP)

13. Clinicians should consider PVP as an option using 120W or 180W platforms for patients for the treatment of LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)

- Generally similar outcomes with regards to symptomatic, urinary improvement in LUTS/BPH and complication rates between TURP and PVP
 - Need continuous irrigation due to high temperatures that may develop
- PVP may be more efficacious for smaller volume prostates
 - Increased probability of intraoperative conversion to TURP for prostate volumes > 60 cc to 80 cc
- Other laser technologies are either investigational or had results that were not considered sufficient or safe to recommend them for routine use

Prostatic Urethral Lift (PUL)

14. Clinicians should consider PUL as an option for patients with LUTS attributed to BPH provided prostate volume <80g and verified absence of an obstructive middle lobe; however, patients should be informed that symptom reduction and flow rate improvement is less significant compared to TURP. (Moderate Recommendation; Evidence Level: Grade C)

- Response and safety favors TURP vs PUL
- IPSS goal reached
 - 91% with TURP
 - 73% with PUL
- Relative risk = 2.7 for serious and non-serious treatment-related harms
- Incontinence favors PUL vs TURP
 - 1.7% vs 17.1%

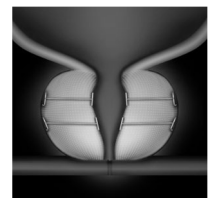


www.ponathanwaginsmd.com

PUL Preservation of Sexual Function

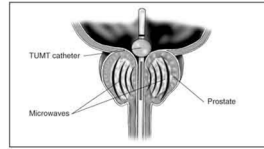
15. PUL may be offered to eligible patients concerned with erectile and ejaculatory function for the treatment of with LUTS attributed to BPH. (Conditional Recommendation; Evidence Level: Grade C)

- Sexual function of men with normal or moderate ED at baseline was unaffected, and those with severe ED reported modest improvement



Transurethral Microwave Therapy (TUMT)

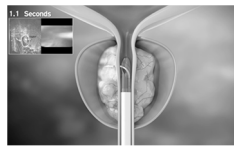
16. TUMT may be offered to patients with LUTS attributed to BPH; however, patients should be informed that surgical retreatment rates are higher compared to TURP. (Conditional Recommendation; Evidence Level: Grade C)



<http://bestmicrowave.hubspace.org/7847/microwave-surgery-for-prostate.html>

Water Vapor Thermal Therapy

17. Water vapor thermal therapy may be offered to patients with LUTS attributed to BPH provided prostate volume <80g; however, patients should be informed that evidence of efficacy, including longer-term retreatment rates, remains limited. (Conditional Recommendation; Evidence Level: Grade C)



- Improvement in I-PSS was 74% with water vapor thermal therapy vs 31% with sham treatment
- Serious AEs were similar between therapy and sham groups
 - Incidence of non-serious transient adverse events was significantly higher in the water vapor thermal therapy group (dysuria, hematuria, frequency and urgency, and UTI)

Water Vapor Thermal Therapy and Sexual Function

18. Water vapor thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)

- Short term: few harms occurred in the water vapor thermal therapy group between months 3 and 12
 - 2% experienced a decrease in ejaculatory volume
- Long-term:
 - No de novo ED was reported
 - No significant changes in IIEF-EF scores or ejaculatory functions
 - Bother associated with ejaculation was assessed was significantly improved at 12 and 24 months following treatment

Transurethral Needle Ablation (TUNA)

19. TUNA is not recommended for the treatment of LUTS attributed to BPH. (Expert Opinion)

- TUNA reduces prostatic volume less than initially anticipated
 - BPH histologic architecture is likely replaced in part with scar
- Lack of peer-reviewed publications
 - Decreasing clinical relevance
- Attempts to identify favorable candidates for TUNA have been unsuccessful

Laser Enucleation

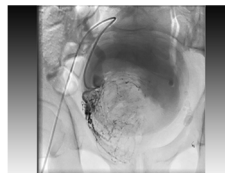
20. Clinicians should consider holmium laser enucleation of the prostate (HoLEP) or thulium laser enucleation of the prostate (ThuLEP), depending on their expertise with either technique, as prostate size-independent suitable options for the treatment of LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)

- Superficial penetration, excellent coagulative properties
- Outcomes measures generally similar to TURP
 - Q_{max} , reoperation, safety, post-surgical complications
 - Less need for blood transfusion with HoLEP or ThuLEP



Prostate Artery Embolization (PAE)

21. PAE is not recommended for the treatment of LUTS attributed to BPH outside the context of a clinical trial. (Expert Opinion)



- Newer, largely untested MIST for BPH
- Available trial results present conflicting picture, relative to TURP
 - Small trials
 - No difference in outcomes, or TURP superiority.

http://img.medscape.com/news/2015/nih_150312_prostatic_artery_embolization_800x600.jpg

Medically Complicated Patients

Patients Receiving Anti-Coagulant Therapy

22. HoLEP, PVP, and ThuLEP should be considered in patients who are at higher risk of bleeding, such as those on anti-coagulation drugs. (Expert Opinion)

- Need for a blood transfusion (either peri- or post-operatively) was significantly less likely with HoLEP and ThuLEP, as compared to TURP
- Superficial penetration, shallow coagulation zones
- PVP is safe and effective for patients who continue their anticoagulant/antiplatelet therapy



Future Directions

Future Directions

Disease Etiology

- No good animal models available

Management of Nocturia

- unique symptom complex requiring special concern and judicious evaluation

Urodynamic Evaluation and Imaging

New Therapeutic Options

- Many new, promising options

Treatment Failure

Treatment Comparative Efficacy

Kristen R. Scarpato, MD MPH
August 8, 2018

- I have no disclosures

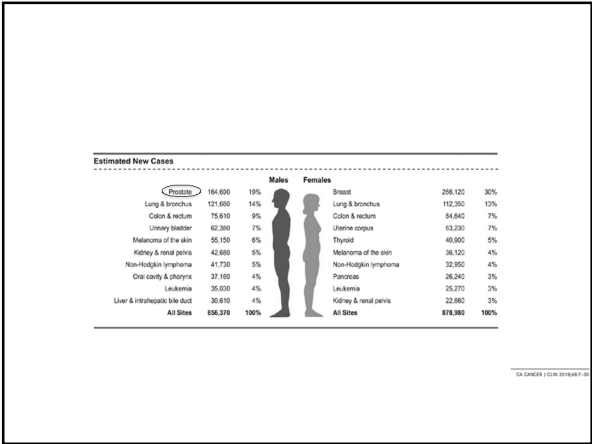
Objectives

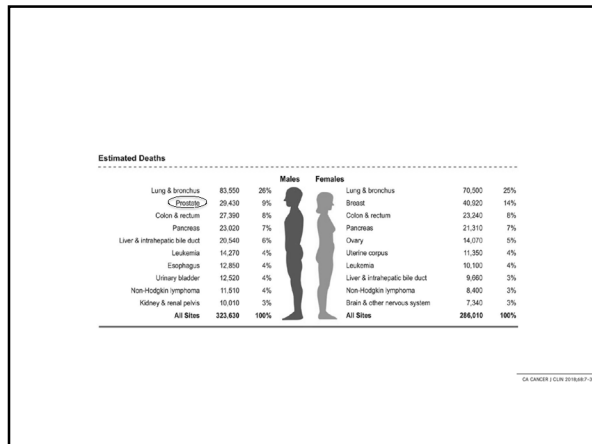
- At the conclusion of this presentation the participant should be able to:
 - Describe goals of screening
 - Understand the history of PSA as a screening tool
 - Be familiar with non-PSA screening tools
 - Describe current recommendations for prostate cancer screening

- # Outline
- Prostate cancer statistics
 - General screening principles
 - PSA Screening
 - Impact of decreased PSA screening
 - Non-PSA Screening tools
 - Current recommendations AUA, NCCN, USPSTF

- Prostate cancer statistics
- General screening principles
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PROSTATE CANCER STATISTICS

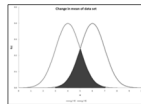




SCREENING

What is A Good Screening Test?

- Sensitive
- Specific
- Non-invasive and safe
- Detects a common condition
- Detects a harmful condition
- Detects a condition that has an effective treatment, which works better in the pre-clinical phase than after the condition is clinically detected
- Cost-effective
- Benefits outweigh harms



Adapted from James McKiernan of Columbia University

What is PSA?

- Glycoprotein produced by epithelial cells of prostate gland
- Normally low levels in serum
- Trauma, infection, inflammation, malignancy results in a larger amount of PSA in serum
- Therefore, serves as a marker for prostate disease
- (PSA is not a cancer-specific marker)

PSA Screening

- PSA correlates with risk of prostate cancer
- The Prostate Cancer Prevention Trial (PCPT) found that normal DRE and...
 - PSA ≤ 4.0 $\rightarrow$ 15% had prostate cancer
 - PSA 4-10 $\rightarrow$ 30 - 35% had prostate cancer
 - PSA > 10 $\rightarrow$ $> 67\%$ likelihood of prostate cancer.

PSA Screening

- Early PSA era $\rightarrow$ screen all, treat all
- Current $\rightarrow$ limit screening, limit treatment
- *Controversial!!*

PSA Screening

Benefits

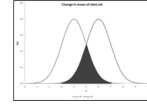
- Reduces risk of dying from prostate cancer

Harms

- Overdiagnosis
- Overtreatment
- Increased cost

Is PSA a Good Screening Test?

- Sensitivity at 4.0 ng/ml = 75%
- Specificity at 4.0 ng/ml = 25%
- Non-invasive and safe yes
- Detects a common condition yes
- Detects a harmful condition yes (but also indolent ca)
- Detects a condition that has an effective treatment, which works better in the pre-clinical phase than after the condition is clinically detected yes (but debated)
- Cost-effective debated
- Benefits outweigh harms debated



Adapted from James McKiernan of Columbia University

Relationship to Incidence

- Cancer incidence impacted by:
 - Risk factors (age, race, family history)
 - behaviors associated with risk
 - *Medical practice* → Screening
- This is particularly relevant in prostate cancer where screening practices have changes based on USPSTF recommendations

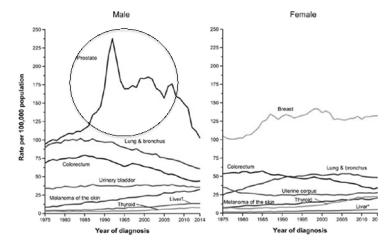
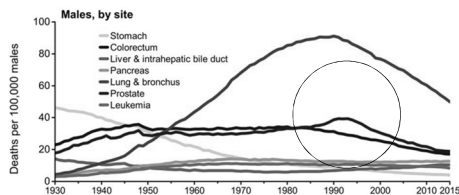


FIGURE 3. Trends in Incidence Rates for Selected Cancers by Sex, United States, 1975 to 2014, age-specific. Rates are age adjusted to the 2000 US standard population and adjusted for delays in reporting. *includes intrahepatic bile duct.

GA CANCER J CLIN 2016;6:67-70



GA CANCER J CLIN 2016;6:67-70

TRIAL DATA

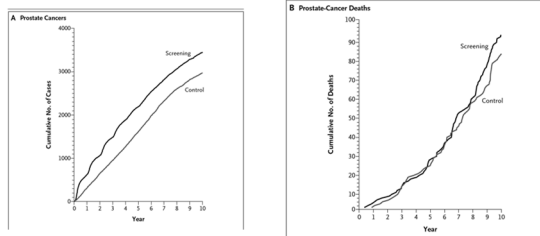
Randomized Screening Trials

- PLCO – no difference in prostate cancer specific mortality with yearly PSA screening
- ERSPC – significant survival benefit from regular PSA screening
- CAP – no difference in mortality with a single PSA screen

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- First report from the PLCO - The US-based randomized screening trial
- 76,693 men aged 55-74
- Routine screening → annual PSA and DRE
- Usual care → control group, patients could elect to screen
- No reduction in PCa-specific mortality associated with screening
- Median follow-up of 10 years

N Engl J Med 2009;360:1310-6



CONCLUSIONS

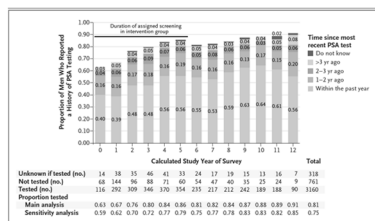
After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. (ClinicalTrials.gov number: NCT00002546)

N Engl J Med 2009;360:1310-6

Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO)

- Significant flaws
- Prescreening with PSA in > 40% of the study subjects
- Contamination (by PSA testing) in 70% of the "unscreened" control cohort

Reevaluating PSA Testing Rates in the PLCO Trial

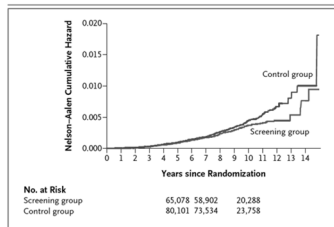


N ENGL J MED 374:18 NEJM.ORG MAY 5, 2016

Screening and Prostate-Cancer Mortality in a Randomized European Study

- The European-based randomized screening trial (ERSPC)
- 182,000 men aged 50-74
- Screening arm – PSA every 4 years
- Control arm – No PSA screening
- Reported statistically significant reduction in relative risk of death from prostate cancer and decreased risk of developing metastatic disease in screening group

N Engl J Med 2009;360:1310-6



CONCLUSIONS
PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis. (Current Controlled Trials number, ISRCTN49127736.)

N Engl J Med 2009;360:1320-8.

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

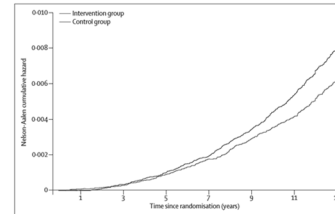


Figure 2: Nelson-Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)

One prostate cancer death averted per 781 men invited for screening
Relative risk reduction in prostate cancer mortality was 27%.

Lancet 2014; 384: 2027-35

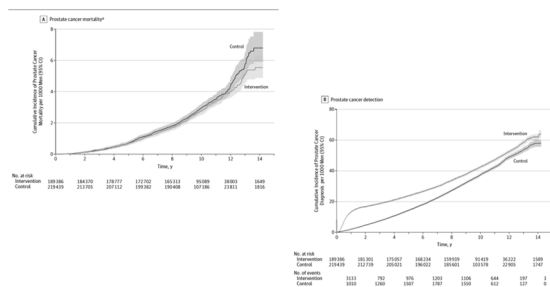
European Randomized Study of Screening for Prostate Cancer (ERSPC)

- Some criticism...
 - Contamination
 - Lower than PLCO
- Variable screening protocols
- Differences in PCa treatment

Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality The CAP Randomized Clinical Trial

- 1^o objective: to evaluate the effect of a single PSA screen and standard work up on PCSM
 - 2^o: stage, grade, all-cause mortality
- Cluster RCT
 - 419,582 men, 2001 – 2009
 - 50 – 69 yrs (59)
- Invited to attend a single PSA testing clinic vs unscreened practice
- Median follow up 10 years

JAMA March 6, 2018 Volume 319, Number 9

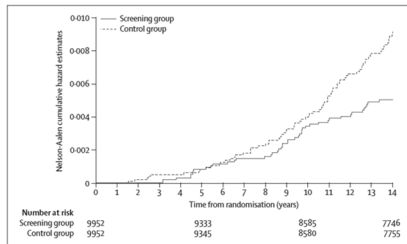


JAMA March 6, 2018 Volume 319, Number 9

Goteborg Trial

- PSA screening trial, randomized
- 20, 000 men age 50 – 64
 - Screening: PSA every 2 years
 - Control: No PSA testing
- Medial follow up 14 years
- Screening significantly reduced the relative risk of death from prostate cancer and decreased risk of being diagnosed with metastases

Lancet Oncol 2010; 11: 725-32



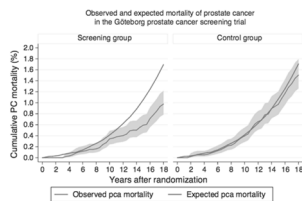
Lancet Oncol 2009; 10: 725-32

Goteborg Study – follow up

- 18 year follow up
- Screened 1369 cases, 79 PCa deaths
- Control 962 cases, 122 PCa deaths
- Findings: organized screening was associated with an absolute PCa specific mortality reduction of 0.72% and relative risk reduction of 42%

EUROPEAN UROLOGY 68 (2015) 354–360

Goteborg Trial



- Organized screening reduces prostate cancer specific mortality

USPSTF RECOMMENDATIONS

USPSTF Recommendations

- **2008:** recommended against routine use of PSA testing (Grade D) in men ages 75 and older
- **2012:** recommended against routine use of PSA testing (Grade D) in all men due to growing concerns regarding overdiagnosis and overtreatment.
- **April 2017:** issued a draft statement revising its recommendation for men aged 55-69 years to informed decision making (Grade C)

CLINICAL GUIDELINES | 17 JULY 2012

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

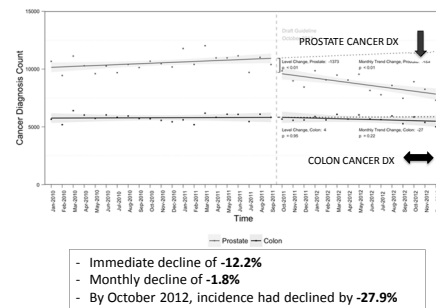
Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	<i>Note:</i> The following statement is an ongoing process. Clinicians may provide this service to selected patients, depending on individual circumstances. However, for most patients without signs or symptoms there is likely to be only a small benefit from this service.	Offer/provide this service only if other considerations support offering or providing the service to an individual patient.
D	The USPSTF recommends against the service. There is moderate to high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

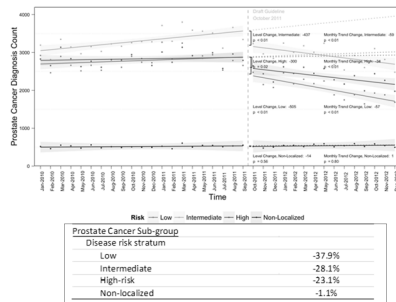
Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States

- National Cancer Database through 2012
- Evaluated rate of new **diagnoses** in the US before and after publication of the USPSTF draft recommendations
- Over 350,000 cases from 1,350 hospitals

Vol. 194, 1587-1593, December 2015



Monthly new diagnoses by D'Amico risk stratum



Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States

- Potential benefits of USPSTF policy
 - Decreased harms of diagnosis and treatment
 - Low risk disease
 - Elderly and infirm
- Potential harms of USPSTF policy
 - Missed opportunities to diagnose and treat
 - Intermediate and high-risk disease
 - Young and healthy
 - Effect on high-risk and vulnerable populations

Vol. 194, 1587-1593, December 2015

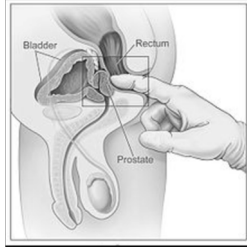
Recent Changes in Prostate Cancer Screening Practices and Epidemiology

- Review of 26 studies on effect of USPSTF
- 2012-2016
- Decrease in PSA testing, prostate biopsy
- Decline in incidence of localized prostate cancer, all risk categories
- Shift towards higher burden of disease at presentation – concern for reverse stage migration

Vol. 198, 1230-1240, December 2017

OTHER SCREENING TOOLS

Digital Rectal Exam



Digital Rectal Exam

- Consider as a baseline tool; complementary
- May detect some clinically significant cancers in patients with normal PSA
- Abnormal DRE increases probability of cancer detection and high grade disease (PCPT, PLCO)
- Should not be used as a stand-alone test
- Low PPV in men with a normal PSA

Biopsy

- Biopsy also a screening tool
- Saturation, transperineal, fusion
- Negative but PSA continues to elevate?
 - Consider multiparametric MRI
- If MRI-visible lesions are present?
 - Consider fusion biopsy
 - The associated prostate cancer risk with a positive mpMRI result is 34-68%

Biomarkers

- Focus on limiting overdiagnosis; improve specificity
- Not yet recommended as first line screening tests
- May be useful if
 - No prior biopsy (%free, PHI, 4K)
 - Prior negative biopsy (PCA3, mpMRI)

Percent-free PSA (%f PSA)

- Majority of PSA circulated bound to proteins
 - Unbound form of PSA, “free”
- FDA approved early detection for PSA 4 – 10
- Significantly lower in men with cancer
- 25% fPSA cutoff detects 95% of prostate cancers while avoiding 20% of unnecessary biopsies

Prostate Health Index (PHI)

- tPSA, fPSA, proPSA
- FDA approved 2012 (PSA 4 – 10)
- Increased sensitivity of prostate cancer detection, discriminates high vs. low grade
- Informs decision to biopsy
- Been shown to decrease biopsy procedures

4Kscore

- tPSA, fPSA, nK2, intact PSA
- Age, DRE, prior biopsy
- Provides estimate of probability of high-grade cancer on biopsy
- High AUC (0.82)
- Informs decision to biopsy
- 65% reduction in prostate biopsies (Konety et al, 2015)

4K score

- Prospective trial
- 1^o outcome: diagnosis ≥ 7 prostate cancer
- 1,012 men scheduled for bx at 26 US Centers
– Oct 2013 – April 2014
- 231 (23%) diagnosed with Gleason ≥ 7
- Outperformed PCPT (AUC: 0.82 vs 0.74)
- Avoid 30-58% biopsies
- Delayed dx of 1–4% Gleason ≥ 7

Parekh et al. Eur Urol 2015

PCA3

- Prostate specific RNA
- Over-expressed in prostate cancer
- Use post DRE urine specimen
- Identify clinically significant PCa
- Data supports use to inform repeat biopsy decision making
– FDA approved for re-biopsy

Prostate MRI

- In men undergoing initial biopsy...
- MRI guided / ultrasound fusion may increase detection of clinically significant cancers
- Lower detection of lower-risk cancers

PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2

- International collaboration
- “Promote global standardization and diminish variation in the acquisition, interpretation and reporting” of prostate mpMRI
- Categories that summarize **levels of suspicion or risk of clinically significant prostate cancer**
- Assist in selection of patients for biopsies and management

EUROPEAN UROLOGY 88 (2016) 16–40

PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2

- Score 1 = highly unlikely (very low)
- Score 2 = unlikely (low)
- Score 3 = equivocal (intermediate)
- Score 4 = likely (high)
- Score 5 = highly likely (very high)
- to have clinically significant PCa

EUROPEAN UROLOGY 88 (2016) 16–40

AUA Policy Statement on the Use of Multiparametric
Magnetic Resonance Imaging in the Diagnosis, Staging
and Management of Prostate Cancer

- Summary of available data re: effectiveness in diagnosis and management
- Provide practical recommendations: screening, diagnosis, staging, surveillance
- Expert review of available + expert consensus in absence of data

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AUA Policy Statement on the Use of Multiparametric
Magnetic Resonance Imaging in the Diagnosis, Staging
and Management of Prostate Cancer

SCREENING

- **NO** evidence support the use of mpMRI for **routine screening**
- Insufficient data for routine use as initial evaluation in biopsy-naïve patients
- Evidence for mpMRI for patients with ***previous negative biopsy and persistent concern for PCa***

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Other biomarkers

- SelectMDx
- ConfirmMDx
- The Mi-Prostate Score (MiPS)
- ExoDx Prostate (IntelliScore)

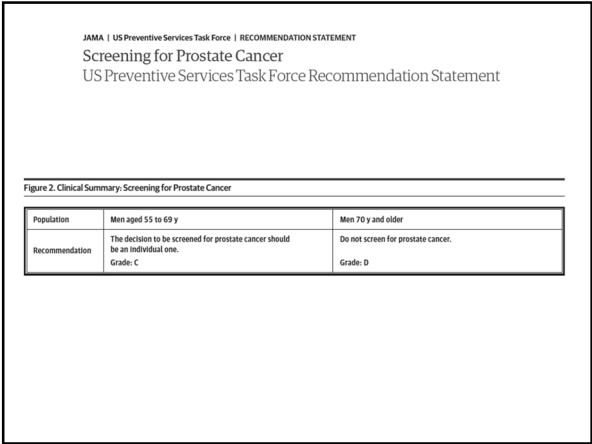
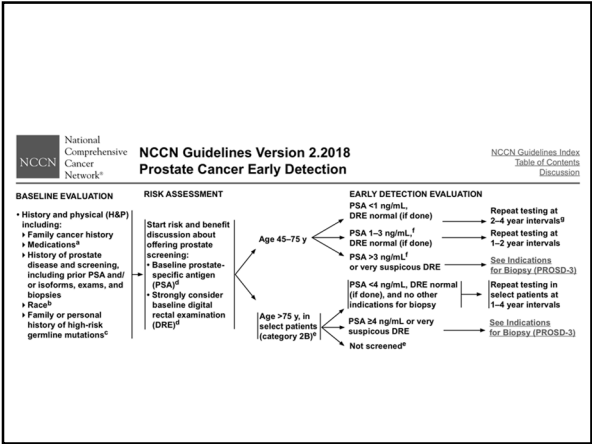
GUIDELINES

Early Detection of Prostate Cancer: AUA Guideline (2013)

- PSA screening in men <40 years is not recommended
- Routine screening in men between the ages of 40 – 54 years at *average risk* is not recommended
- **For men ages 55 – 69, the decision to undergo PSA screening involves shared decision making**
 - *Screening interval of two years or more*
- Routine screening in men >70 or in any man with <10-15 year life expectancy is not recommended

Early Detection of Prostate Cancer: AUA Guideline (2013)

- Intended to be used by urologists as a means of detecting prostate cancer in early, pre-symptomatic men



CONCLUSIONS

Conclusions

- PSA screening remains controversial but decreases risk of death from prostate cancer

Smarter Screening

- Know the facts
- Healthy men / life expectancy
 - Most likely to benefit
- Shared decision making
- Longer screening intervals
- Utilize additional testing when appropriate

Thank You



Disclosures

- Research Grants: NCI, PCF
- Consulting Fees: Lilly
- Conference Travel Expenses: Sanofi

Outline

- Rationale and utilization trends
- Barriers to uptake of active surveillance
- Outcomes of active surveillance

Overdiagnosis and Overtreatment of Prostate Cancer

Stacy Loeb^{a,c}, Marc A. Bjurlin^a, Joseph Nicholson^b, Teuvo L. Tammela^c, David F. Penson^d, H. Ballentine Carter^e, Peter Carroll^f, Ruth Etzioni^g

- Up to 67% cases overdiagnosed depending on the population and criteria
- Historically the vast majority of low-risk patients received radical treatment
 - Overtreatment → unnecessary side effects

Reviews

BJUI
BJU International

The Melbourne Consensus Statement on the early detection of prostate cancer

Declan G. Murphy^{1,2,3}, Thomas Ahlering⁴, William J. Catalona⁵, Helen Crowe^{2,3}, Jane Crowe², Noel Clarke¹⁰, Matthew Cooperberg², David Gillatt¹¹, Martin Gleave¹², Stacy Loeb⁷, Monique Roobol¹⁴, Oliver Sartor⁸, Tom Pickles¹³, Addie Woolfen¹, Patrick C. Walsh⁹ and Anthony J. Costello^{2,3}

- Consensus Statement 2: "Prostate cancer diagnosis must be uncoupled from prostate cancer intervention"

2012 US Preventive Services Task Force (USPSTF) Guidelines

- Grade D recommendation against PSA
 - Per 1000 men screened:
 - 1 fewer prostate cancer death
 - 30-40 men with incontinence or erectile dysfunction due to treatment
 - 2 men with serious cardiovascular events
 - 1 venous thrombosis

www.uspreventiveservicestaskforce.org

2018 USPSTF Recommendations

Population	Recommendation	Grade
Age 55-69	Recommends that clinicians inform men about the potential benefits and harms of screening	C
Age ≥70	Recommends against PSA-based screening	D

Active Surveillance Factored Into Changes in Screening Guidelines

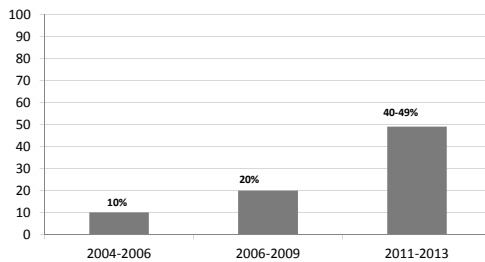
Update of Previous USPSTF Recommendation

This recommendation replaces the 2012 USPSTF recommendation¹⁰ on PSA-based screening for prostate cancer. In 2012, the USPSTF concluded that, although there are potential benefits of screening for prostate cancer, these benefits do not outweigh the expected harms enough to recommend routine screening (D recommendation). The change in recommendation grade is based in part on additional evidence that increased the USPSTF's certainty about the reductions in risk of dying of prostate cancer and risk of metastatic disease. Longer-term follow-up of the ERSPC trial and from some ERSPC trial sites found that PSA-based screening for prostate cancer prevents 1.28 men from dying of prostate cancer for every 1000 men screened. In addition, a subset of ERSPC trial sites have since reported that screening 1000 men aged 55 to 69 years may prevent approximately 3 men from developing metastatic prostate cancer. Longer-term, 12.7-year results of the PIVOT trial became available since the posting of the draft recommendation statement and are similar to the 10-year results. Studies continue to demonstrate the harms of PSA-based screening, including false-positive results, complications from transrectal prostate biopsies, overdiagnosis (which may occur in 20%-50% of cases of screen-detected cancer, based on estimates from trial data), psychological harms, and harms of treatment, including urinary incontinence and erectile dysfunction. The change in recommendation grade further reflects new evidence about and increased use of active surveillance of low-risk prostate cancer, which may reduce the risk of subsequent harms from screening. This recommendation also clearly identifies African American men and men with a family history of prostate cancer as having higher risk for prostate cancer and provides additional information to help support these men in making informed decisions about screening. For the C recommendation for men aged 55 to 69 years, the USPSTF's intention is to convey that each man's values may shift the balance to a net benefit of screening and to promote the importance of informed decision making prior to screening. The USPSTF continues to find that the benefits of screening do not outweigh the harms in men 70 years and older and recommends against screening in these men.

"The change in recommendation grade further reflects new evidence about and increased use of active surveillance of low-risk prostate cancer, which may reduce the risk of subsequent harms from screening."

Reducing Overtreatment in USA (CaPSURE, MUSIC, New Hampshire)

% Observation for Low-Risk Prostate Cancer



Cooperberg 2007, Hoffmann 2014, Ingimansson et al. CCC 2015, Womble et al. Eur Urol 2014, Cooperberg et al. JAMA 2015

The Association Between Evaluation at Academic Centers and the Likelihood of Expectant Management in Low-risk Prostate Cancer

Natanie H. Lester-Coll, Henry S. Park, Charles E. Rutter, Christopher D. Corso, Brandon R. Mancini, Debra N. Yee, Simon P. Kim, Cary P. Gross, and James B. Yu

- National Cancer Database (2010-2013)
 - 70% newly diagnosed cases in USA
 - N=91,556 low risk
- Expectant management use
 - 17% academic centers vs. 8% community centers
 - Multivariable analysis: 2.7x greater at academic centers

Lester Coll et al. Urology 2016

Letters

Use of Conservative Management for Low-Risk Prostate Cancer in the Veterans Affairs Integrated Health Care System From 2005-2015

Loeb S, Byrne N, et al.

Published online May 15, 2018

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

The JAMA Network

JAMA Journal of the American Medical Association

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Use of Conservative Management for Low-Risk Prostate Cancer in the Veterans Affairs Integrated Health Care System From 2005-2015

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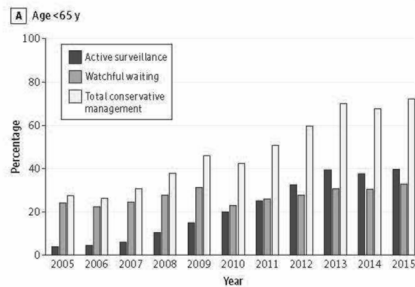
Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

Methods

- From 2005-2015, n=125,083 US veterans diagnosed with low-risk PCa (PSA<10, Gleason ≤6, cT1/T2a)
- Sub-classification of AS vs. watchful waiting using codes
 - AS if ≥2 PSA and 1 biopsy within 2 years after diagnosis, otherwise classified as WW
- Statistical analysis:
 - Cochrane-Armitage test used to examine trends in conservative management use over time, stratified by age
 - Multivariable logistic regression used to identify predictors of conservative management vs. treatment, and AS vs. WW

Loeb et al. JAMA 2018; 319 (21).

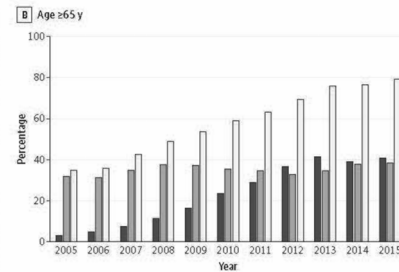
Increasing Uptake of Conservative Management in US Veterans Age <65



- Dramatic increase from 27% in 2005 to 72% in 2015
- AS increased from 4% to 39%

Loeb et al. JAMA 2018; 319 (21).

Increasing Uptake of Conservative Management in US Veterans Age ≥65



- Dramatic increase from 35% in 2005 to 79% in 2015
- AS increased from 3% to 41%

Loeb et al. JAMA 2018; 319 (21).

Conservative Management in VA: Conclusion

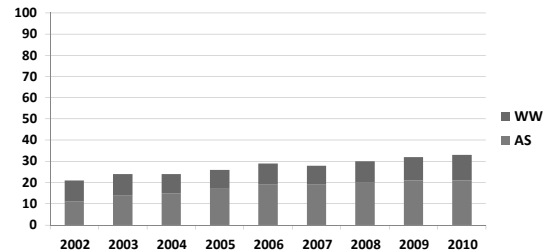
- Conservative management uptake has increased significantly in a nationwide sample of U.S. veterans with low-risk prostate cancer
- These results suggest a substantial reduction in overtreatment during the past decade, and compare favorably with prior U.S. studies in different healthcare settings

Loeb et al. JAMA 2018; 319 (21).

The uptake of active surveillance for the management of prostate cancer: A population-based analysis

Patrick O. Richard, MD,^{1,2} Shabbir M.H. Alibhai, MD,² Tony Panzarella, MD,⁴ Laurence Klotz, MD,⁴ Maria Komisarenko, MD,¹ Neil E. Fleshner, MD,² David Urbach, MD,² Antonio Finelli, MD²

- Population-based study of men with localized prostate cancer in Ontario
- AS use increased from 11% in 2002 to 21% in 2010



Richard et al. CUAJ 2016; 10: 333

World J Urol
DOI: 10.1007/s00345-016-1897-0

ORIGINAL ARTICLE

Analysis of active surveillance uptake for low-risk localized prostate cancer in Canada: a Canadian multi-institutional study

Narhari Timilshina¹ · Veronique Ouellet¹ · Shabbir M. H. Alibhai¹ · Anne-Marie Mes-Masson² · Nathalie Delvoye³ · Darrel Drachenberg⁴ · Antonio Finelli¹ · Marie-Paule Jammal⁵ · Pierre Karakiewicz^{2,3} · Hélène Lapointe⁶ · Jean-Baptiste Lattouf^{2,3} · Kenny Lynch⁷ · Jean-Benoît Paradis⁴ · Paula Sitarik⁸ · Alan So⁹ · Fred Saad^{2,3}

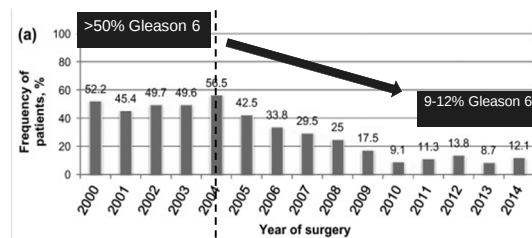
- Multi-institutional Canadian study of incident low-risk cases in 2010 (6 centers in 4 provinces)
- 77% received AS for initial management
 - Significant variation across centers: 65–98% ($p=0.001$)
 - 85% remained on AS at 12 months (64–94% by center)

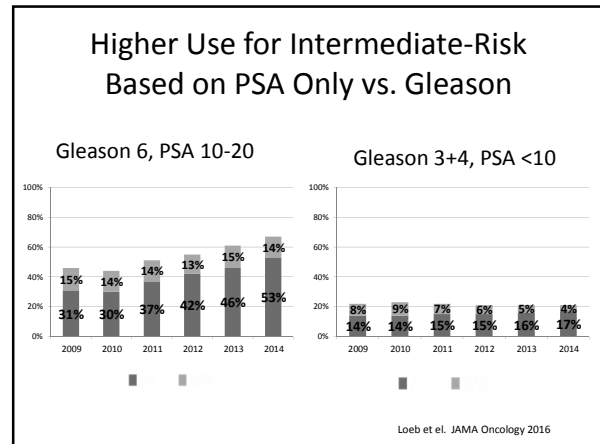
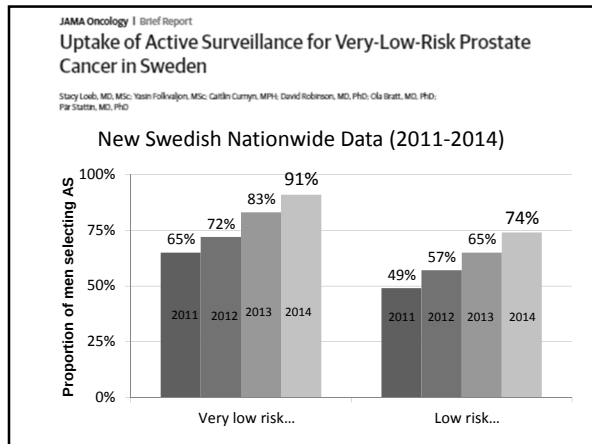
Brief Correspondence

Changing Trends in Surgical Management of Prostate Cancer: The End of Overtreatment?

Hartwig Huland, Markus Graefen^{*}

Martin-Clinic Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany





Active Surveillance Guidelines

JOURNAL OF CLINICAL ONCOLOGY **ASCO SPECIAL ARTICLE**

Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline); American Society of Clinical Oncology Clinical Practice Guideline Endorsement

- **Recommended management** for most low-risk patients (Gleason ≤ 6)
- **May be offered** to select patients with low-volume, intermediate-risk PCa (Gleason 3+4=7)
- Watchful waiting more appropriate if <5 year life expectancy

Chen et al. JCO 2016 epub.

2017 AUA/ASTRO/SUO Guideline: Clinically Localized Prostate Cancer

Very Low Risk

- Clinicians should recommend active surveillance as the best available care option (*Strong Recommendation; Evidence Level A*)

Low Risk

- Clinicians should recommend active surveillance as the preferable care option (*Moderate Recommendation; Evidence Level B*)
- Clinicians may offer definitive treatment (i.e. radical prostatectomy or radiotherapy) to select patients who may have a high probability of progression (*Conditional Recommendation; Evidence Level B*)

Intermediate Risk

- Active surveillance may be offered to select patients with *favorable* intermediate-risk localized prostate cancer; however, patients should be informed that this comes with a higher risk of developing metastases compared to definitive treatment (*Conditional Recommendations, Evidence Level C*)

2018 National Comprehensive Cancer Network Guidelines

- Very low-risk
 - Observation if life expectancy <10y
 - AS if life expectancy 10-20y
 - AS/RT/RP if life expectancy $\geq 20y$
- Low-Risk and Favorable intermediate-risk:
 - Observation if life expectancy <10y
 - AS/RT/RP if life expectancy $\geq 10y$

2018 European Association of Urology Position Statement

- Include all men with low-risk PCa
 - Men with life expectancy >20 yr should be properly counseled about the lack of very long-term data of AS
- Low-volume GG2: Increased risk of progression and metastasis
 - Informed consent about lack of robust data
- Consider central pathological review of biopsy specimens when commencing long-term conservative management

Outline

- Rationale and utilization trends
- Barriers to uptake of active surveillance
- Outcomes of active surveillance

Challenge 1:

Barriers to Uptake
-Patients
-Physicians

Increasing Patient Acceptance of AS- Renaming “Gleason 6” Disease

- “Cancer” is an emotion-laden term but Gleason 6 has limited metastatic potential
 - Proposals to remove “cancer” label- NOT adopted
- New grade groups adopted reclassifying 6-10 as 1-5

Traditional Gleason score	Grade group
6	1
3+4=7	2
4+3=7	3
8	4
9-10	5

Epstein et al. Eur Urol 2016 epub

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



Research Letter

Perspectives of Prostate Cancer Patients on Gleason Scores and the New Grade Groups: Initial Qualitative Study

Stacy Loeb^{a,b,c,*}, Caitlin Curnyn^b, Erica Sedlander^b

- 80% of patients feel more comfortable with active surveillance for “grade group 1” vs “Gleason 6”

Barriers to AS Uptake: Biopsy Risks

- Low and favorable intermediate-risk CaP in SEER-Medicare data (2009-2011)
- Significantly lower uptake of AS in men with complications on diagnostic biopsy

Adamsky et al. AUA 2017

BJUI
BJU International

Qualitative study on decision-making by prostate cancer physicians during active surveillance

Stacy Loeb^{*,1,2,5}, Caitlin Cumyn¹, Angela Fagerlin^{6,*,*}, Ronald Scott Braithwaite¹, Mark D. Schwartz^{1,5}, Herbert Lepor^{*,7}, Herbert Ballentine Carter¹¹ and Erica Sedlander¹

- In-depth interviews with US prostate cancer providers until thematic saturation was reached (n=24)
- Transcripts were independently coded by 2 researchers
- Matrix analysis and NVivo software used for organization and further analysis

Increasing Acceptance of AS- Qualitative data on Challenges for US Providers

- **Varying experience/exposure to AS during training**
 - “We train people to do something. We are by nature doers and AS is not really part of what a surgeon is wired to do.”
- **Concerns about inflicting “harm” and legal risk**
 - “It’s possible that you miss the window of curability on your watch. They could be hurt by that choice. That’s a lot of responsibility.”
 - “There’s obviously some degree of liability.”
- **Financial incentives**
 - “In Europe where there is no fee for service system the uptake of AS is exponentially higher than it is in the U.S.”

Loeb et al. BJUI 2016 epub.

Challenge 2:

Risk of upfront misclassification

Optimizing Patient Selection

- PSA, clinical stage and standard biopsy result in substantial rates of misclassification (>1/3)
- Substantial biologic heterogeneity within broad risk groups
- Role for imaging and biomarkers to refine selection

Shapiro & Johnstone Urology 2012; 80: 661. Loeb et al. Eur Urol 2013 epub. Lee et al. Can J Urol 2010; 17: 5429. Ross et al. JCO 2010; 28: 2810.

Genomic Tests for Risk Stratification

	Company	Reported Endpoints	Technique	Sample
Oncotype DX	Genomic Health	Adverse pathology (+Mets, PCa death)	RT-PCR	Highest grade tumor
Prolaris	Myriad	PCa death (+Mets w Tx)	RT-PCR	Largest tumor
Decipher	GenomeDx	Metastasis (+High grade, PCa death)	Microarray	Highest grade tumor

Genomic Testing

AUA Guidelines (2017)

Among most low-risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance. (Expert Opinion)

NCCN(2018)

¹Men with low or favorable intermediate risk disease may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, Prolaris, Promark. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. See Discussion.

 Ontario Health Technology Assessment Series

Ontario Health Technology Assessment Series 2017; 17(6): 1-75
Published online 2017 May 1

Prolaris Cell Cycle Progression Test for Localized Prostate Cancer: A Health Technology Assessment

Health Quality Ontario

- No evidence on clinical outcomes of patients whose treatment was informed by Prolaris
- Economic evaluation for publicly funding Prolaris
 - Net budget impact= \$41.3M in 5y (mostly from cost of the test)
 - \$7.3 million estimated savings by increasing AS insufficient to offset high cost
- Patients viewed the test as potentially helpful but were unsure it would ultimately change their treatment choice

Predictors of Reclassification and/or Metastatic Disease During AS

- Patient factors
 - African American
 - Obesity
- Risk classification (Intermediate > Low > Very low)
 - PSA density >0.15
 - Greater extent of cancer on biopsy
 - Gleason $\geq 3+4=7$ (>3x greater risk of metastasis)

Loeb et al. Eur Urol 2015; 67: 619. Yamamoto et al J Urol 2016; 195: 1409.
Bhindi et al Eur Urol 2014; 66: 841

Challenge 3:

Monitoring Protocols

Monitoring During AS- NCCN

 National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018 Prostate Cancer

Active surveillance*

- PSA no more often than every 6 mo unless clinically indicated
- DRE no more often than every 12 mo unless clinically indicated
- Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
- Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative

Monitoring During AS- EAU 2018

- PSA at least once every 6 months
- DRE at least once a year
- Repeated biopsy at a minimum interval of 3-5 years
- mpMRI cannot be used as a stand-alone tool to trigger follow-up biopsies

 BJUI International

Urological Oncology

Qualitative study on decision-making by prostate cancer physicians during active surveillance

Stacy Loeb BSc, Caitlin Curry, Angela Fagerlin, Ronald Scott Braithwaite, Mark D. Schwartz, Herbert Lepor, Herbert Ballentine Carter, Erica Sedlander

Key Themes to Explain Heterogeneity in AS Practices

- Physician comfort with AS
- Protocol selection
- Beliefs about utility and quality of testing
- Years of experience and AS exposure in training
- Concerns about inflicting harm
- Patient characteristics
- Patient preferences
- Financial incentives

Challenges with Monitoring During AS

VOLUME 28 • NUMBER 17 • JUNE 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prostate-Specific Antigen Kinetics During Follow-Up Are an Unreliable Trigger for Intervention in a Prostate Cancer Surveillance Program

Ashley E. Ross, Stacy Loeb, Patricia Landis, Alan W. Partin, Jonathan I. Epstein, Anna Ketterer, Zhanyong Feng, H. Ballentine Carter, and Patrick C. Walsh

- Changes in PSA not reliable (AUC 0.59 for biopsy reclassification)
- Guidelines still recommend routine surveillance biopsy every 1-5 years

Challenges with Monitoring During AS

- MRI is not recommended as a replacement for repeated prostate biopsy
- Biopsy-based AS presents significant risks and patient burden
 - ↑ infections over time due to antibiotic resistance
 - Other risks: bleeding, pain, urinary symptoms, possible erectile dysfunction
 - Source of noncompliance

Ross et al. JCO 2010; 28: 2810. Nam et al. J Urol 2010; 183: 963. Loeb et al. J Urol 2011; 186: 1830. Loeb et al. Eur Urol 2013; 64: 876.

Biopsies During AS (SEER-Medicare)

Tests received by 1349 men on AS for 5y	% of patients
PSA	
≥5 PSA (yearly)	91%
≥10 PSA (2x/yr)	59%
Biopsy	
≥2 biopsies	34%
≥3 biopsies	15%
Combination	
≥10 PSA + ≥2 biopsies	22%

Strategies to improve adherence:

- More tools/resources to support men on AS
- More noninvasive testing options (e.g. markers and MRI)
- Individualizing the protocol based upon risk factors

Loeb et al. J Urol 2016 epub.

Markov Model: Design

Comparison of Conservative Management Strategies in the Model

Watchful Waiting	No testing. No treatment unless metastatic disease.
AS- Johns Hopkins	PSA every 6 months and annual biopsy. Treat if grade progression on biopsy.
AS- PRIAS	PSA every 3 months. Repeat biopsy after 1, 4, and 7 years. Treat for grade progression.
AS Exploratory-MRI Based	PSA every 6 months and yearly MRI. Biopsy if MRI is positive. Treat for grade progression.
AS-5 year biopsy	PSA every 6 months and biopsy every 5 years. Treat if grade progression.

Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x-y of this issue

Active Surveillance Versus Watchful Waiting for Localized Prostate Cancer: A Model to Inform Decisions

Stacy Loeb^{a,b}, Qinlan Zhou^a, Uwe Siebert^{a,d,e,f}, Ursula Richau^a, Beate John^a, Nikolai Mühlberger^a, H. Ballentine Carter^a, Herbert Lepor^a, R. Scott Braithwaite^b

Model starting at 50yo	Incremental life-years	Incremental quality-adjusted life-years	Lifetime metastasis	Lifetime prostate cancer death
Watchful waiting	---	--	10.3%	8.7%
AS- Hopkins (1yr bx)	+0.66	+0.53	6.4%	5.4%
AS- PRIAS (bx yrs 1,3,7,10)	+0.57	+0.44	7.1%	6.0%
AS- MRI-based	+0.65	+0.53	6.4%	5.4%
AS- Biopsy every 5y	+0.44	+0.27	8.2%	6.9%

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Stacy Loeb^{a,b}, Qinlan Zhou^a, Uwe Siebert^{a,d,e,f}, Ursula Richau^a, Beate John^a, Nikolai Mühlberger^a, H. Ballentine Carter^a, Herbert Lepor^a, R. Scott Braithwaite^b

	Incremental QALY- 40yo	Incremental QALY- 50yo	Incremental QALY-65yo	Incremental QALY-70
Watchful waiting	--	--	--	--
AS- Hopkins	+0.89	+0.53	-0.10	-0.31
AS- PRIAS	+0.73	+0.44	-0.10	-0.28
AS- MRI-based	+0.90	+0.53	-0.10	-0.32
AS- Biopsy q5y	+0.49	+0.27	-0.13	-0.18

• Among men aged >65 yr, AS still had a small increase in life-years but WW had more QALYs

DOI: 10.1002/pro.2202
ORIGINAL ARTICLE

WILEY **The Prostate**

When should active surveillance for prostate cancer stop if no progression is detected?

Tiago M. de Carvalho MSc¹ | Eveline A. M. Heijnsdijk PhD¹ | Harry J. de Koning PhD

- Microsimulation model based on Hopkins AS
- Low-risk patients:
 - Ages 55-65: AS is cost-effective for up to 7 yearly biopsy rounds
 - Age >65: Even 1 biopsy round results in QALYs lost
- Intermediate-risk:
 - AS is cost-effective even at ages 65-75

Outline

- Rationale and utilization trends
- Barriers to uptake of active surveillance
- Outcomes of active surveillance

The **NEW ENGLAND JOURNAL of MEDICINE**
ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oleson, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group¹

- Active “monitoring” with PSA kinetics
 - More men developed metastases
 - No difference in prostate cancer death

Long-Term Outcomes of Sunnybrook AS (Canada)

- n=993 enrolled since 1995
 - 79% low risk, 21% intermediate risk
- Treatment-free: 76% at 5y, 64% at 10y, 55% at 15y
- 30 (3%) developed metastasis, 15 Pca deaths (1.5%)
- At 15 years:
 - 94% cancer-specific survival
 - *9x more likely to die from other causes vs prostate cancer*

Klotz et al. JCO 2016; 33: 272
Yamamoto et al. J Urol 2016; 195: 1409.

Long-Term Outcomes of Hopkins AS (USA)

- N=1298 enrolled since 1995
 - 71% very low risk, 29% low-risk PCa
- Treatment-free: 63% at 5y, 50% at 10y, 43% at 15y
- At 15 years:
 - 99.4% metastasis-free survival
 - 99.9% PC-specific survival
 - *24x more likely to die of other causes than to develop metastasis or death from prostate cancer*

Tosoian et al. JCO 2015; 33: 3379.

AS in Goteborg Screening Trial (Sweden)

- N=474 managed by AS (no predefined protocol)
 - 51% very low, 27% low, 22% intermediate-risk
- % treatment free: 47% at 10y, 34% at 15y
- At 15 years:
 - 93% metastasis-free survival
 - 96% cancer-specific survival
 - 100% very low risk, 96% low risk, 90% intermediate-risk
 - 51% overall survival

Godman et al. Eur Urol 2016 epub.

Modeling Studies of AS

- Compared to initial treatment, AS is associated with:
 - Slightly higher rate of prostate cancer death
 - 2.8% at 20 years (AS), versus 1.6% (treatment)
 - Greater quality-adjusted life-expectancy
 - Lower costs

Xia et al. Clin Cancer Res 2012; 18: 5471. Hayes et al. JAMA 2010; 304: 2373. Eldefrawy et al. Urol Oncol 2013; 31: 576.

Conclusion

- Increasing use of active surveillance worldwide
 - Persistent variability and barriers to uptake
- Recommended option for low-risk prostate cancer
 - Majority remain on surveillance >5y
 - Low rate of metastasis within 15y
 - Greater risk of death from other causes than PCa
 - Cost-effective
- Future improvement with greater personalization and integration of noninvasive tests

Prostate Cancer Biomarkers

Todd M. Morgan, MD
Associate Professor
University of Michigan

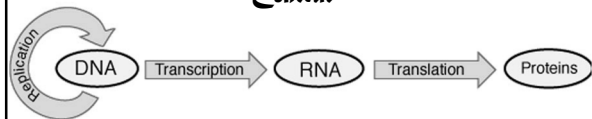
Disclosures

- Myriad Genetics: Research funding, advisory board
- MDxHealth: Research funding, advisory board
- GenomeDx: Research funding

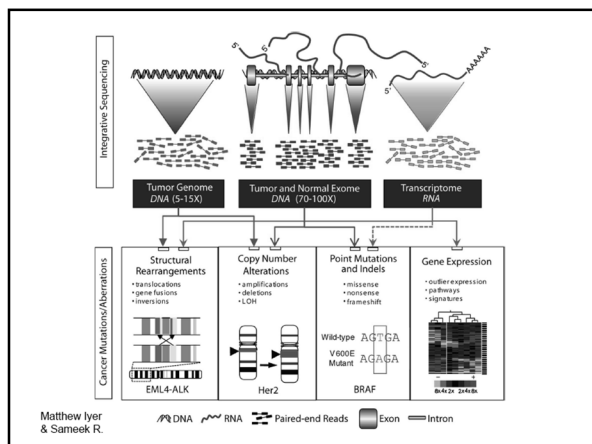
Definitions

- Genetics: Study of single/limited number of genes and their functions
 - Often used to refer to heritable mutations
- Genome: All of the genes in an individual
- Genomics: Study of the genome
- Epigenetics: Study of changes to DNA that don't involve change in nucleotide sequence
- Proteomics: Large-scale study of proteins

**My Karma
Ran Over
Your Dogma**
Central



- 2% of genome codes for protein
- 98% “dark matter”
 - Majority of dark matter still transcribed (lncRNA, miRNA, piRNA. . .)



Why do we care? Biomarkers can help with. . .

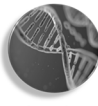
- Risk assessment: what is the probability of disease?
- Screening: can earlier diagnosis affect outcome?
- Diagnosis: is the disease present?
- Prognosis: what is the likely outcome?
- Prediction: outcome in the presence of specific treatment?
- Monitoring: is therapy working?

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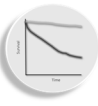
Personalization of Therapy

Prognostic vs Predictive Biomarkers

- Nearly all cancer biomarkers are **prognostic** biomarkers that provide information on outcomes *independent of the treatment received*
- A **predictive** biomarker specifically identifies response or resistance to a particular therapy – but *not all treatments*.
- Both** are used to personalize therapy



Elucidate Biology
Develop new therapies



Prognostic Biomarker
Understand risk of recurrence



Predictive Biomarker
Guide treatment selection

M UROLOGY

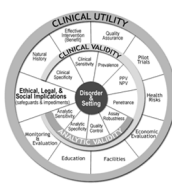
The ideal biomarker

- Safe and easy means of assessment
- Optimal statistical associations with intended outcome (e.g., high sensitivity, specificity, positive and negative predictive value)
- Provides clinically useful information that guides decision making

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Process for evaluating biomarkers

- Analytical validity:** does the assay accurately measure what it is intended to measure
- Clinical validity:** does the assay identify a clinically relevant biological difference
- Clinical utility:** do the results of the assay impact the plan of care and improve outcomes



M UROLOGY

EDRN approach to validation

Figure 1 Guiding Principles for Biomarker Research: Phases of Early Detection Research



- Phase 1 Preclinical Exploratory**
Exploratory studies to identify potentially useful biomarkers
- Phase 2 Clinical Assay and Validation**
Studies to determine the capacity of biomarkers to distinguish between people with cancer and those without
- Phase 3 Retrospective Longitudinal**
Determine how well biomarkers detect preclinical disease by testing the markers against tissues collected longitudinally from research cohorts
- Phase 4 Prospective Screening**
Identify the extent and characteristics of disease detected by the test and determine the false referral rate
- Phase 5 Cancer Control**
Evaluate both the role of the biomarkers for detection of cancer and the overall impact of screening on the population through large-scale population studies

M UROLOGY

Assessing performance of diagnostic tests

- Validity of a diagnostic test refers to its ability to measure what it is purported to measure.

Table 1. Standard table for comparison of test results with actual disease status

	Disease Present	Disease Absent	
Test Positive	a (true positives)	b (false positives)	a+b
Test Negative	c (false negatives)	d (true negatives)	c+d
	a+c	b+d	a+b+c+d

Sensitivity = $a / (a+c)$
 Specificity = $d / (b+d)$
 Accuracy = $a+c / (a+b+c+d)$
 Positive Predictive Value = $a / (a+b)$
 Negative Predictive Value = $d / (c+d)$

From Penson/Wei ed: Clinical Research Methods for Surgeons 2006

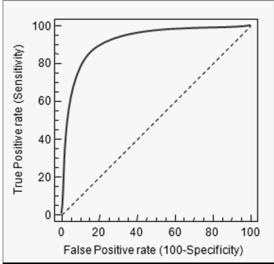
M UROLOGY

PPV and NPV are key

- Positive Predictive Value (PPV):** Given that a test is positive, PPV is the probability that this patient actually has the disease
- Negative Predictive Value (NPV):** Given that a test is negative, NPV is the probability that this patient actually does not have the disease

M UROLOGY

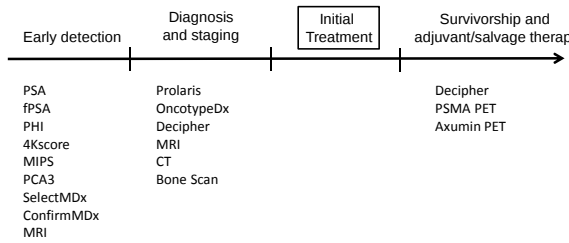
What is an ROC curve?



- How good is the test at finding the truth?
- Tests have false positives and false negatives
- $\uparrow$ AUC = Better Test

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Prostate Cancer Continuum of Care (localized disease)



Early detection	Diagnosis and staging	Initial Treatment	Survivorship and adjuvant/salvage therapy
PSA fPSA PHI 4Kscore MIPS PCA3 SelectMDx ConfirmMDx MRI	Prolaris OncotypeDx Decipher MRI CT Bone Scan		Decipher PSMA PET Axumin PET

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Sources of prostate cancer biomarkers

- Urine
 - Can be post-DRE
- Blood
 - Few currently used markers outside of PSA and PSA derivatives
- Sputum
 - Source for germline DNA
- Tissue
 - Biopsy or surgical specimen (FFPE)

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Early Detection

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PSA

- Secreted protein first studied in 1970s
- Serine protease (kallikrein 3)
- Secreted into semen
- Mature PSA comes from 2 proteolytic cleavages (pre-proPSA and proPSA)

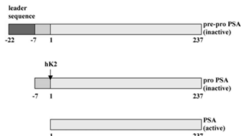


Figure 1 Molecular structure of pre-pro-PSA, pro-PSA, and PSA.

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PSA performance characteristics

- Screening:
 - Specificity: 20-40%
 - Sensitivity: 70-90%
 - AUC 0.55-0.70
- Key flaw is confounding by BPH and variability between tests
 - Similar expression by BPH and PCa cells

PSA derivatives

- PSA velocity (PSAV): Cutoff of 0.75 ng/ml/yr sometimes used in screening setting
- PSA doubling time (PSADT): <http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx>
- PSA density (PSAD): Cutoff of 0.15 ng/ml/cc often used
- Age-specific PSA cutoffs (2.5, 3.5, 4.5, 6.5 ng/ml)

Free PSA

- Unbound PSA (α 1-antichymotrypsin)
- Lower %fPSA/tPSA = higher PCa risk
- FDA approved for use in patients with PSA of 4-10 ng/ml (Catalona et al, 1998 JAMA)

Rates of prostate cancer			
Free:total PSA ratio	50-59 years	60-69 years	≥70 years
≤0.10	49.20%	57.50%	64.50%
0.11-0.18	26.90%	33.90%	40.80%
0.19-0.25	18.30%	23.90%	29.70%
>0.25	9.10%	12.20%	15.80%

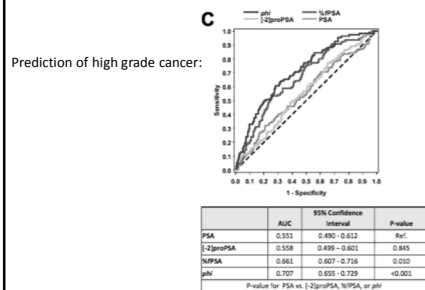
Prostate Health Index (PHI)

- Source: Blood
- Assay: Combines PSA, fPSA, [-2]proPSA

$$- \left(\frac{[-2]proPSA}{fPSA} \right) \times \sqrt{PSA}$$
- FDA approved for PCa diagnosis in patients with PSA 4-10 ng/ml
- [-2]proPSA is precursor to active PSA

The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer

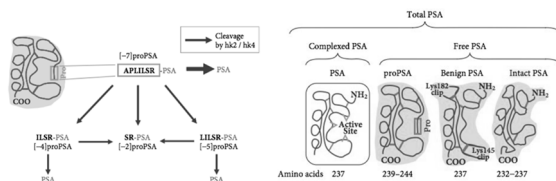
Stacy Loeb,*† Martin G. Sanda,† Dennis L. Broyles,§ Sanghyuk S. Shin,§ Chris H. Bangma,|| John T. Wei,* Alan W. Partin,|| George G. Klee,§ Kevin M. Slawin,§ Leonard S. Marks,|| Ron H. N. van Schalk,|| Daniel W. Chan,|| Lori J. Sokol,|| Amabelle B. Cruz,§ Isaac A. Mitrabhi§ and William J. Catalona**



Loeb et al., 2015 J Urol

4Kscore

- Source: Blood
- Assay: Combines total PSA, fPSA, intact PSA, and hK2



A Multi-institutional Prospective Trial in the USA Confirms that the 4Kscore Accurately Identifies Men with High-grade Prostate Cancer

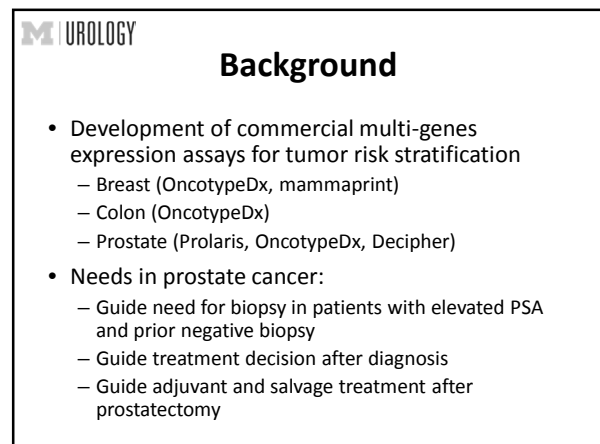
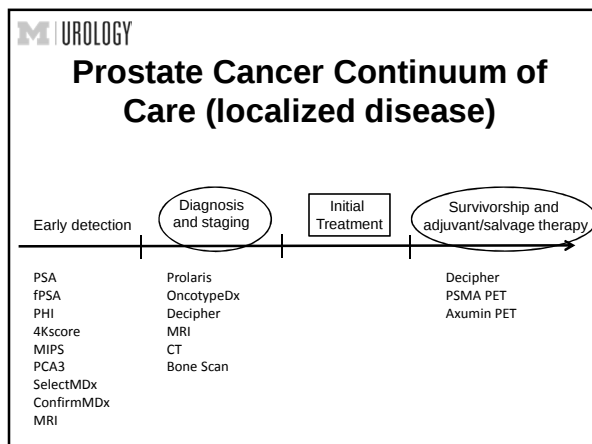
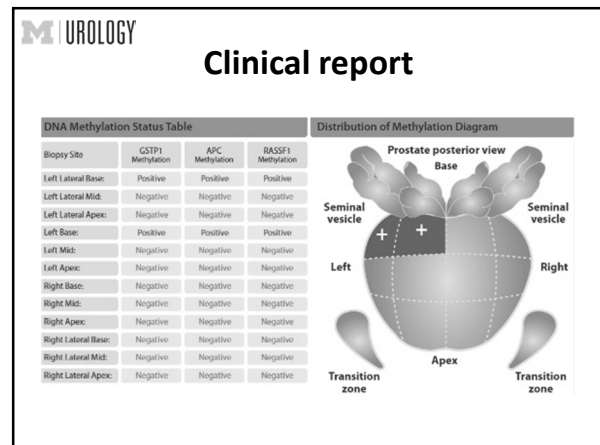
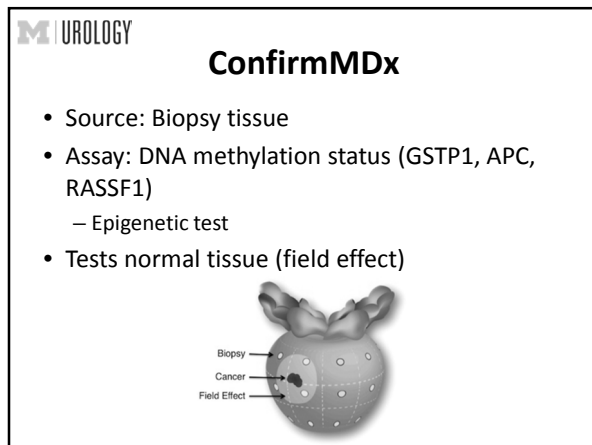
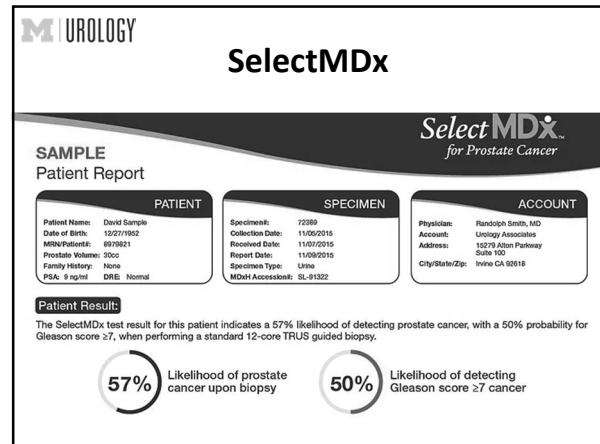
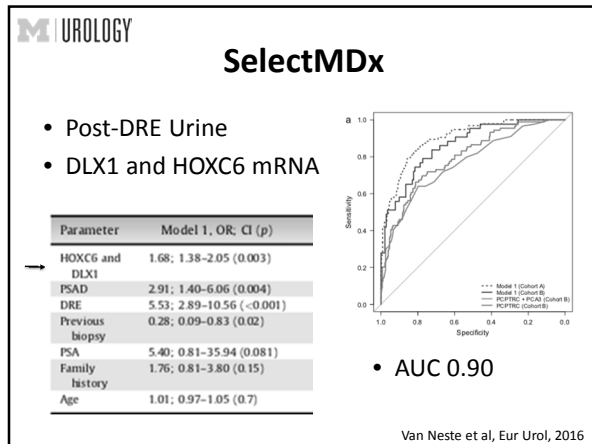
Dipen J. Parekh*, Sanjay Ponnuru*, Daniel D. Sjoberg*, Scott W. Aschaff*, James L. Bailin*, James S. Cochran*, Raulo Conception*, Richard D. David*, Kenneth B. Deek*, Igor Dambadar*, Michael Gambino*, Michael S. Grizzle*, Ralph J. Henderson*, Lawrence Karsh*, Evan B. Krusch*, Timothy D. Langford*, Daniel W. Lin*, Sharon M. McGee*, John J. Muro*, Christopher M. Piazonka*, Kimberly Rieger-Christ*, Daniel R. Saltzman*, John W. Scott*, Neal D. Shore*, Paul R. Sieber*, Todd M. Waldmann*, Fredrick N. Wolk*, Stephen M. Zappala**

Table 2 – Discrimination of Gleason ≥ 7 cancer using the full 4Kscore and a model without each individual kallikrein

	AUC (95% CI)	Difference	p value
Full model	0.821 (0.790, 0.852)		
Model without total PSA	0.655 (0.616, 0.694)	0.167	<0.0001
Model without free PSA	0.699 (0.664, 0.735)	0.122	<0.0001
Model without intact PSA	0.794 (0.760, 0.828)	0.027	0.001
Model without hK2	0.806 (0.774, 0.839)	0.015	0.020
Model without intact PSA and hK2	0.751 (0.714, 0.789)	0.070	<0.0001

AUC = area under the receiver operating characteristic curve; CI = confidence interval; PSA = prostate-specific antigen; hK2 = human kallikrein 2.

Parekh et al, Eur Urol, 2014



TISSUE-BASED GENE EXPRESSION CLASSIFIERS (GECs)

DECIPHER

(GenomeDx Biosciences): Microarray 22 RNA biomarkers on a scale of 0-1

Threshold: Low vs high risk = 0.45/0.60

ONCOTYPE DX

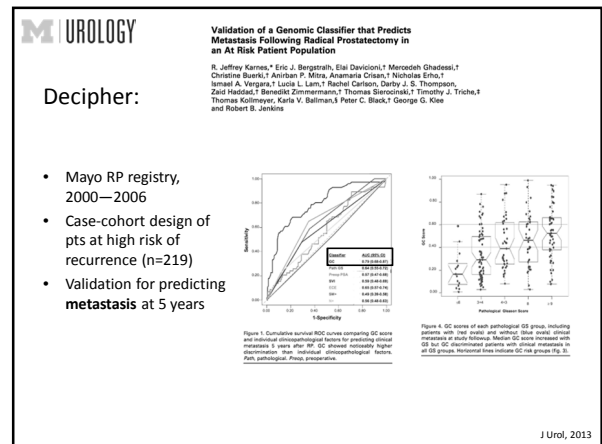
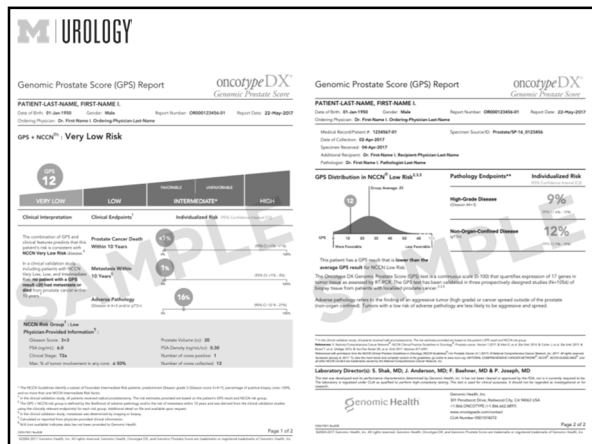
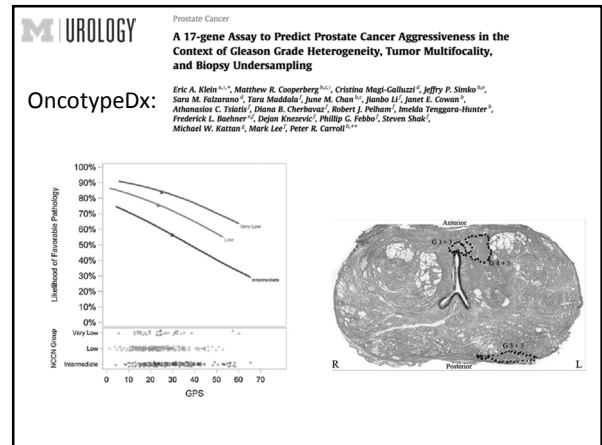
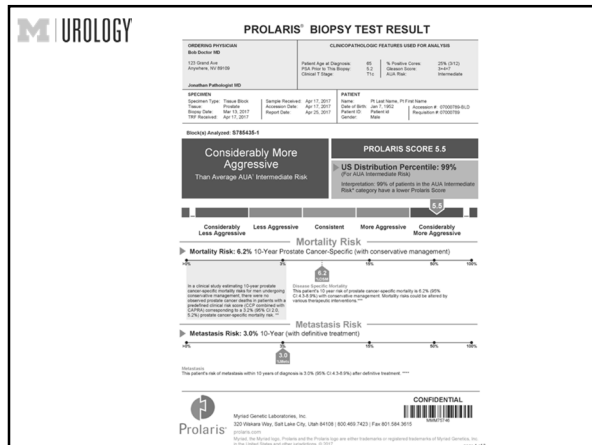
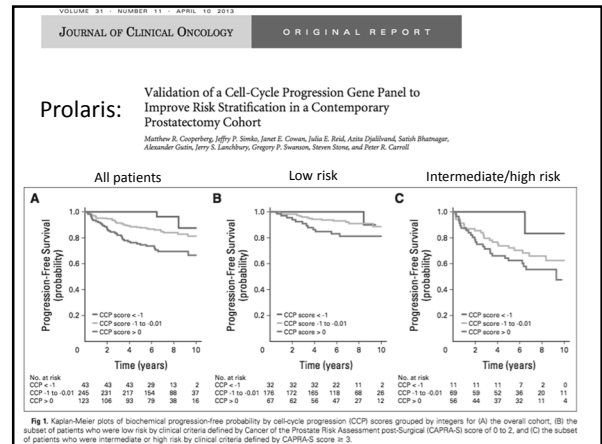
(Genomic Health): Quantitative real-time PCR 17 genes on a scale of 0-100

Threshold: Low vs high risk = probability of adverse surgical pathology >20%

PROLARIS

(Myriad Genetics): Quantitative real-time PCR 46 genes on a scale of 1-10

Threshold: Low vs high risk = 10 year mortality risk ≥ 3.2%



Radiation Therapy
Robert E. Den, Karen Tancif, Edmund J. Trabulsi, Huse Abdallah, Volod Chourong, Felix Y.

-

Salvage RT	36	17	4	Salvage RT	60	27	9
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Patient Details	Order Information
First Name:	Order Date:
Middle Initial/Last Name:	Insurance Reason Code:
Date of Birth:	Insurance Reason Code Description:
Date of Procedure:	Ordering Physician:
Referring Physician:	Ordering Facility:
Pathologist:	Ordering Department:
Address:	Additional Physician:

Clinical Details	Preoperative PSA (ng/mL)	Gleason Score	% Positive Nodes	Tertiary Disease
PSA:	4.3	4+3	NR	Yes
PSAD:	0.17	0.17	NR	No

POST OP

Your Decipher Result – Genomic High Risk

Risk Level	Decipher Score 0.7	Risk - Percent Likelihood
High Risk	5-Year Metastasis	10.4%
Ambiguous	5-Year Mortality	11.4%
Low Risk	15-Year Prostate Cancer Specific Mortality	11.4%

Interpretation

Clinical studies conducted suggest that Decipher High risk men with active pathways have a poor prognosis overall.¹⁻³ These men may benefit from adjuvant or early salvage resection and consideration for clinical trials.

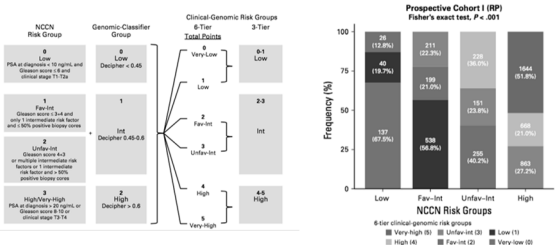
Research findings have published that patients with Decipher High risk have a 71% 5-year mortality rate survival and 30% 15-year cause specific survival.⁴ Fewer than 60% have been shown to survive beyond 10 years following adjuvant and endocrine therapy.

In patients with PSA or biochemical recurrence after surgery that required salvage radiotherapy, only 38.3% remained alive after 5 years.⁵

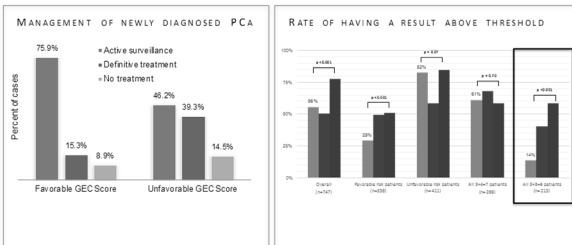
Sullivan et al., JCO 2014; 32(15):2433-2440

David E. Swartz, Jiechun Zhang, Maria Santiago-Simón, Robert T. Den, John W. Davis, Robert B. Den, Ad

Daniel E. Spratt, Jinglin Zhang, Maria Santiago-Jimenez, Robert T. Dem, John W. Davis, Robert B. Dem, Adam Dicker, Christopher J. Kane, Alan Pollack, Radika Stoyanova, Frans Abdillahi, Ashley E. Ross, Adam Cole, Ed Utkin, Josh M. Rendell, Hae Nyeon, Shuang G. Zhao, Rohit Mehra, Andrew G. Glass, Lucia L. de Lame, Joon Chellieran, Marguerite de Fleiss, Vishal Choudhary, Maria Ales, Tyler Kulinski, Jennifer Margenau, Jason J. Jennifer Jordan, Christine Buehli, Karu Yousefi, Zaid Haddad, Eli Devickson, Edward J. Treibolt, Stacy J. Ashworth-Treadwell, Peter R. Carroll, Sheila Weissman, Edward M. Schaeffer, Eric A. Klein, R. Jeffrey Korman, Fei Feng, and Paul L. Nyeon



- Favorable risk patients: 58% on AS if no GEC test



Hu, J., Spratt DE and Morgan TM. JCO Prec Onc. 2018.

```

graph LR
    A[Newly diagnosed prostate cancer, considering active surveillance] --> B[MRI]
    B -- "If negative result" --> C[MRIUS fusion biopsy]
    B -- "If positive result" --> D[Confirmatory TRUS biopsy]
    C --> E[Very low risk]
    C --> F[Low risk]
    C --> G[Intermediate risk]
    C --> H[High risk]
    D --> E
    D --> F
    D --> G
    D --> H
    E --> I[Low-intensity active surveillance]
    F --> I
    G --> J[Genomic testing (ProstateSeq, OncotypeDX)]
    H --> J
    I <--> J
    J -- "If needed, OAT" --> K[Standard active surveillance]
    J --> L[Primary treatment]
  
```

The flowchart illustrates the proposed management algorithm for newly diagnosed prostate cancer, considering active surveillance. It begins with a box labeled "Newly diagnosed prostate cancer, considering active surveillance", which leads to a box labeled "MRI". From "MRI", two paths emerge: "If negative result" leading to "MRIUS fusion biopsy", and "If positive result" leading to "Confirmatory TRUS biopsy". Both biopsy boxes lead to four risk categories: "Very low risk", "Low risk", "Intermediate risk", and "High risk". "Very low risk" and "Low risk" lead to "Low-intensity active surveillance". "Intermediate risk" and "High risk" lead to "Genomic testing (ProstateSeq, OncotypeDX)". There is a bidirectional arrow between "Low-intensity active surveillance" and "Genomic testing". From "Genomic testing", a path labeled "If needed, OAT" leads to "Standard active surveillance", and another path leads to "Primary treatment".

```
graph TD
    A[Patient undergoing RP for clinically localized prostate cancer] --> B{{Final pathology = PT3+ and/or positive surgical margins}}
    B --> C[PSA <0.1 ng/ml]
    C --> D[Consent]
    D --> E[RANDOMIZATION 1:1 cluster-crossover in 3 month blocks]
    E --> F[Decipher test not performed (gene expression studies performed at a later date for end of study analyses)]
    E --> G[Decipher test performed (at no cost to patient or insurer 2-4 weeks from enrollment)]
    F --> H[CAPRA-S score reviewed with patient]
    G --> I[Decipher and CAPRA-S score reviewed with patient]
    H --> J[patient/provider choice]
    I --> K[patient/provider choice]
    J --> L((Adjuvant XRT))
    J --> M((Observation))
    K --> N((Adjuvant XRT))
    K --> O((Observation))
```

The flowchart illustrates the study design for the CAPRA-S trial. It begins with patients undergoing radical prostatectomy (RP) for clinically localized prostate cancer. The study includes a selection criterion based on final pathology (PT3+ and/or positive surgical margins) and a PSA level less than 0.1 ng/ml. After obtaining consent, patients are randomized in a 1:1 cluster-crossover design over 3-month blocks. The randomization leads to two groups: one where the Decipher test is not performed (with gene expression studies performed later) and another where the Decipher test is performed (at no cost to the patient or insurer, 2-4 weeks from enrollment). Both groups have their CAPRA-S score reviewed with the patient. The patient then chooses between adjuvant XRT and observation, with the provider also having a choice.

UROLOGY

Advanced Prostate Cancer

UROLOGY

Predictive Biomarker:
AR Splice Variant-7 (AR V7)

PSA Responses by AR-V7 Status

AR-V7 is a truncated form of the AR that lacks the ligand-binding domain, but remains constitutively active as a transcription factor.

PFS by AR-V7 Status

Antonarakis ES et al. N Engl J Med 2014

UROLOGY

Original Investigation

Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

Howard I. Scher, MD, David Lu, PhD, Nicole A. Schreiber, BA, Jessica Loken, BS, Ryan P. Gray, PhD, Herbert A. Vargas, MD, Ann Johnson, MS, Adam Jendrusak, MBA, Richard Barbour, MS, BC, SMD, David Caruso, MD, Nigel McLaughlin, MD, Justin West, BS, Stephen B. Gonen, PhD, Glen Heller, PhD, Dana Marinucci, PhD, Martin Fleisher, PhD, Ryan Ottomaro, MBA

A) AR-V7 positive single CTCs

B) AR-V7 negative single CTCs

C) Overall survival: pre-AR signaling inhibitor samples

UROLOGY

DNA-repair defects in advanced PCa

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Castells, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, B. Longo, M. Hussain, A. Chinnaiyan, J. Vinton, J. Filipek, L. Garraway, M.E. Taplin, S. Adubayan, G.C. Han, M. Sengul, C. Montesion, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H. Schar, C. Samyans, N. Schultz, P.W. Kantoff, D. Salt, M. Rubin, E.M. Van Allen, E. Orlitzky, J. de Bono, and P.D. Nelson

Figure 2. Distribution of Presumed Pathogenic Germline Mutations.

Shows are mutations involving 18 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

• 11.8% of men with metastatic PCa had germline mutations in DNA repair genes

Pritchard, NEJM, 2016

UROLOGY

PCa risk estimates by mutation

Gene	Risk for PCA	Risk for aggressive PCA features	Risk for early-onset PCA (age at diagnosis <65)	Risk for PCSM
BRCA1	1.07–3.81	—	1.82	5.16
BRCA2	3.18–8.6	3.18–4.38	7.33	2.4–5.48
Mismatch repair genes	1.99–3.67	—	2.48	—
HOXB13	2.8–8.47	—	2.7–10.11	—

Giri, Sem Oncol, 2016

UROLOGY

Localized PCa in germline BRCA+ patients is more aggressive

EAU

Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localized Prostate Cancer

Elisei Gattuso^{1,2,3}, Cher Goh⁴, David Longpremont⁵, Ed Sander⁶, M. Gormley⁷, J. Kishor⁸, J. Kishor⁹, J. Kishor¹⁰, J. Kishor¹¹, J. Kishor¹², J. Kishor¹³, J. Kishor¹⁴, J. Kishor¹⁵, J. Kishor¹⁶, J. Kishor¹⁷, J. Kishor¹⁸, J. Kishor¹⁹, J. Kishor²⁰, J. Kishor²¹, J. Kishor²², J. Kishor²³, J. Kishor²⁴, J. Kishor²⁵, J. Kishor²⁶, J. Kishor²⁷, J. Kishor²⁸, J. Kishor²⁹, J. Kishor³⁰, J. Kishor³¹, J. Kishor³², J. Kishor³³, J. Kishor³⁴, J. Kishor³⁵, J. Kishor³⁶, J. Kishor³⁷, J. Kishor³⁸, J. Kishor³⁹, J. Kishor⁴⁰, J. Kishor⁴¹, J. Kishor⁴², J. Kishor⁴³, J. Kishor⁴⁴, J. Kishor⁴⁵, J. Kishor⁴⁶, J. Kishor⁴⁷, J. Kishor⁴⁸, J. Kishor⁴⁹, J. Kishor⁵⁰, J. Kishor⁵¹, J. Kishor⁵², J. Kishor⁵³, J. Kishor⁵⁴, J. Kishor⁵⁵, J. Kishor⁵⁶, J. Kishor⁵⁷, J. Kishor⁵⁸, J. Kishor⁵⁹, J. Kishor⁶⁰, J. Kishor⁶¹, J. Kishor⁶², J. Kishor⁶³, J. Kishor⁶⁴, J. Kishor⁶⁵, J. Kishor⁶⁶, J. Kishor⁶⁷, J. Kishor⁶⁸, J. Kishor⁶⁹, J. Kishor⁷⁰, J. Kishor⁷¹, J. Kishor⁷², J. Kishor⁷³, J. Kishor⁷⁴, J. Kishor⁷⁵, J. Kishor⁷⁶, J. Kishor⁷⁷, J. 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M UROLOGY

Predictive Biomarker: DNA repair defects (DRD)

- DNA repair pathway genes include BRCA1, BRCA2, ATM, and CHEK2
- PARP inhibitors work by targeting PARP1, an enzyme which repairs single strand breaks.

PARP Mechanism and Inhibition

DNA Damage → PARP → PAR Chain → DNA Repair → Cell Survival

NAD⁺ → PARP Inhibition → Inactivated PARP → DNA Collapse → Apoptosis

BER indicates base excision repair; NAD, nicotinamide adenine dinucleotide.

M UROLOGY

TOPARP Trial: Olaparib (PARP-I) and Association with Defects in DNA-Repair Genes

A Radiologic Progression-free Survival
P<0.001 by log-rank test
Biomarker-positive, median: 9.8 mo
Biomarker-negative, median: 2.7 mo

B Overall Survival
P=0.05 by log-rank test
Biomarker-positive, median: 13.8 mo
Biomarker-negative, median: 7.5 mo

- Phase 2 trial, heavily pretreated CRPC (n=50)
- Tumor DRD associated with response

Mateo J et al. N Engl J Med 2015

Individualized Therapy Based on Molecular Enrichment (Any Histology)

Molecular Eligibility?

PIK3CA mut	PI3K inhibitor
CDK6 amp	CDK inhibitor
FGFR1 amp	FGFR inhibitor
AR amp	Anti-androgen
TCL1A	AKT inhibitor
PI3KR2 mut	PI3K inhibitor
PTEN del	PI3K inhibitor
DDR mut	PARP-I

Tumor Genomic Analysis

- 1) Molecular enrichment and eligibility
- 2) Endpoints: Response Rate
- 3) Comparison of primary responders versus non-responders
- 4) Pre-treatment and Post-resistance biopsy: mechanisms of resistance

M UROLOGY

Summary

- Know what's available in each disease setting
- Consider whether additional information will impact decision
- Understand what each test is predicting
- Distinction between prognostic and predictive markers is key
- Be critical of data with each new test that is commercialized and marketed

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Prostate Cancer – Utilization of MRI for Screening, Diagnosis, and Management

Mohammad Minhaj Siddiqui, MD
Associate Professor of Surgery
Director of Urologic Oncology and Robotic Surgery, University of Maryland Medical System

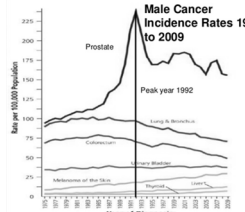
Disclosures

No disclosures

Prostate cancer

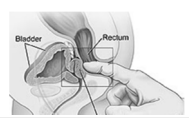
- Most common cancer in men
 - 233,000 new cases in the US in 2014
 - 1 in 6 men will be diagnosed with prostate cancer in their life

Second leading cause of cancer death in US men



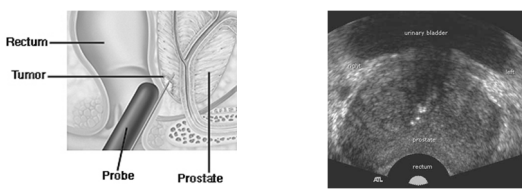
How is prostate cancer diagnosed?

- PSA (prostate-specific antigen)
 - PSA produced in normal prostate and prostate cancer
 - Cancer makes much more than normal prostate
 - High levels raise suspicion for cancer
- Digital rectal exam
 - Doctor feels the surface of the prostate gland for nodules, hard spots, and any other abnormalities



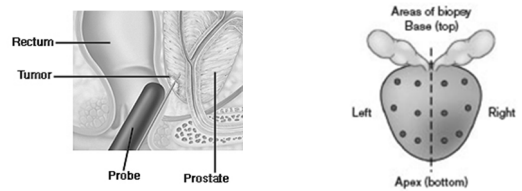
Prostate biopsy

Next step if PSA is high (>4ng/ml) or rectal exam is abnormal is prostate biopsy



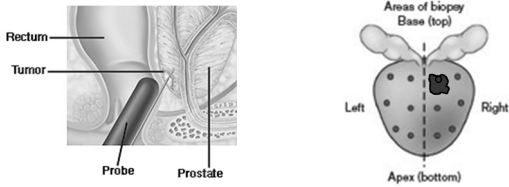
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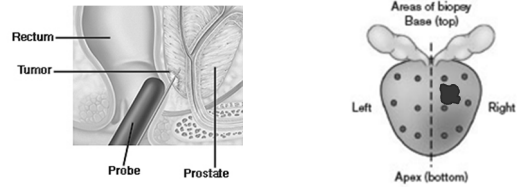
Prostate biopsy

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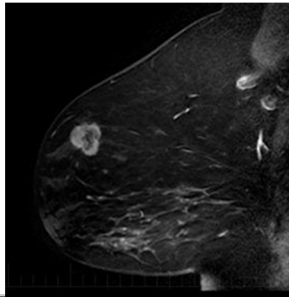


Prostate biopsy

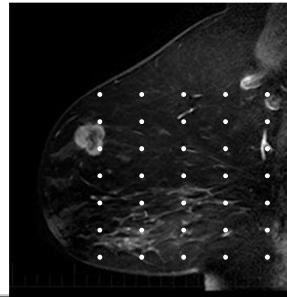
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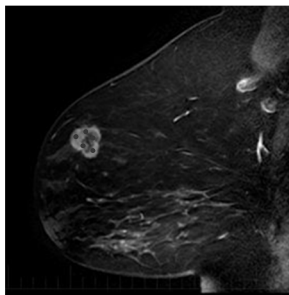
Why do we still rely on random sampling to diagnose prostate cancer?



Why do we still rely on random sampling to diagnose prostate cancer?



Why do we still rely on random sampling to diagnose prostate cancer?



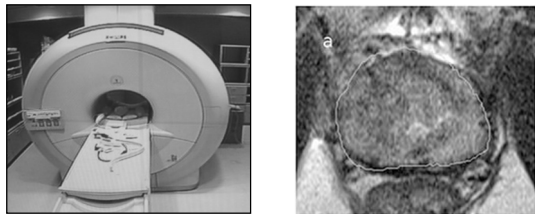
Rationale of adding imaging

Prostate cancer is the only solid tumor that is diagnosed by randomly sampling the organ in the hopes of hitting the tumor

Linked to the lack of reliable imaging for localizing tumors within the prostate

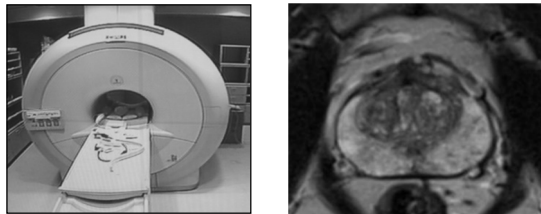
Can advances in MRI and other imaging modalities change this?

Multi-parametric Prostate MRI



Older technology MRI

Multi-parametric Prostate MRI

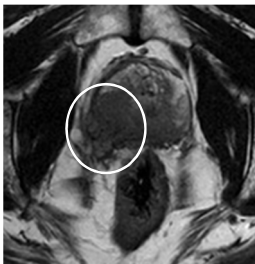


Newer 3.0 Tesla MRI

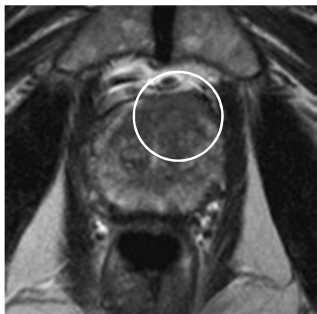
Sample MRIs



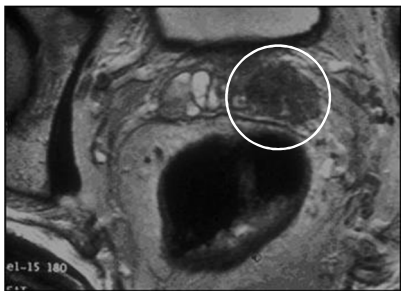
Sample MRIs



Sample MRIs



Sample MRIs



Multi-parametric Prostate MRI

T2W:

Measures water content

Tumors are water poor (dark on T2W)

DWI: Diffusion Weighted Imaging

Measures water diffusion in tissue

Tumors are dense (dark on DWI)

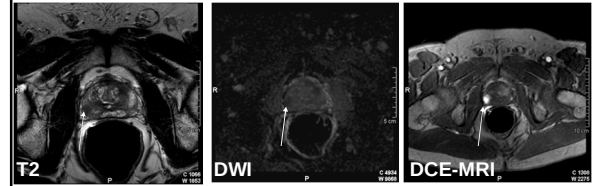
DCE: Dynamic Contrast Enhanced

Measures contrast flow through tissue

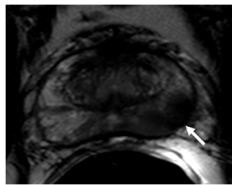
Tumors are hypervascular (bright on DCE)



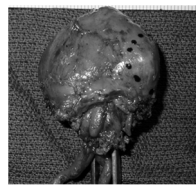
Multi-parametric 3T Endorectal MR Imaging of the Prostate



Cutting edge topic in 2012: Do MRI findings predict prostatectomy pathology?



?=

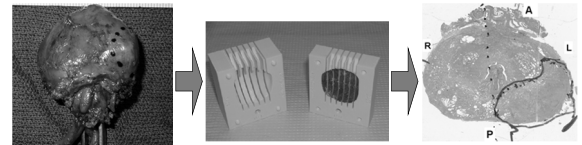


CHALLENGE: How do you cut the prostate in the exact same plane as the MRI image?



Turkbey, et al., Correlation of magnetic resonance imaging tumor volume with histopathology, J Urol. 2012 Oct;188(4):1157-63.

Cutting edge topic in 2012: Do MRI findings predict prostatectomy pathology?

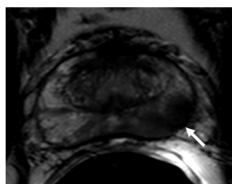


ANSWER: 3D Print a custom mold for every prostatectomy case with slits to cut specimen in plane of MRI images

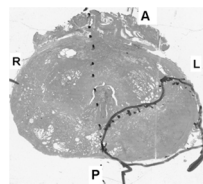


Turkbey, et al., Correlation of magnetic resonance imaging tumor volume with histopathology, J Urol. 2012 Oct;188(4):1157-63.

Cutting edge topic in 2012: Do MRI findings predict prostatectomy pathology?



?=



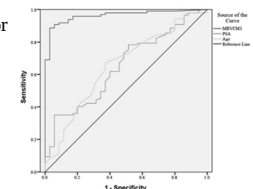
Turkbey, et al., Correlation of magnetic resonance imaging tumor volume with histopathology, J Urol. 2012 Oct;188(4):1157-63.

Cutting edge topic in 2012: Do MRI findings predict prostatectomy pathology?

Correlation of Magnetic Resonance Imaging Tumor Volume with Histopathology

Baris Turkbey,* Haresh Mani,* Omer Aras,* Ardeshtir R. Rastinehad,* Vijay Shah,† Marcelino Bernardo,* Thomas Pohida,* Dagane Daer,* Compton Benjamin,* Yolanda L. McKinney,* W. Marston Linehan,* Bradford J. Wood,† Maria J. Merino,* Peter L. Choyke* and Peter A. Pinto*,§

- MRI accurate in detection of tumor lesions $>0.5 \text{ cm}^3$
- 88% sensitive
- 95% specific
- Even better performance for Gleason score ≥ 7



Turkbey, et al., Correlation of magnetic resonance imaging tumor volume with histopathology, J Urol. 2012 Oct;188(4):1157-63.

PIRADS

Prostate Imaging and Reporting and Data System

ESUR prostate MR guidelines 2012

- Guidelines for MRI in PCa
- Clinical indications, minimal/optimal MRI techniques
- PI-RADS structured reporting system
 - Rates the likelihood of the presence of clinically significant prostate cancer
 - Score of 1-5 for T2, DWI/ADC, DCE, MRS,extra-prostatic

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Barentsz JO et al. European Radiology 2012;22:746-57

PIRADS v2

Prostate Imaging and Reporting and Data System

PIRADS v2 introduced at RSNA 2014

Promote standardization, decrease variation in acquisition, interpretation and reporting

Improve detection, localization, characterization, risk stratify

More specific criteria for T2 and DWI scoring

- PZ: DWI is dominant sequence
- TZ: T2 is dominant sequence

MRS is not included in scoring

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PIRADS v2, ACR

T2 - Peripheral Zone

1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity. Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

T2 - Transition Zone

1	No abnormality (i.e. normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI
4	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

PIRADS v2

Overall Peripheral Zone				
DWI	T2	DCE	PIRADS	
1	Any	Any	1	
2	Any	Any	2	
3	Any	-	3	
		+	4	
4	Any	Any	4	
5	Any	Any	5	

DWI - PZ and TZ

1	No abnormality (i.e. normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI
4	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

DCE - Peripheral and Transition Zone

(-) no early enhancement, or diffuse enhancement not corresponding to a focal finding on T2 and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2WI
(+) focal, and; earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and, corresponds to suspicious finding on T2W and/or DWI

Overall Transition Zone

T2	DWI	DCE	PIRADS	
1	Any	Any	1	
2	Any	Any	2	
3	≤4	Any	3	
5	Any	Any	4	
4	Any	Any	4	
5	Any	Any	5	

PIRADS v2 Assessment Categories

PIRADS 1 – Very low (clinically significant cancer is highly unlikely to be present)

PIRADS 2 – Low (clinically significant cancer is unlikely to be present)

PIRADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)

PIRADS 4 – High (clinically significant cancer is likely to be present)

PIRADS 5 – Very high (clinically significant cancer is highly likely to be present)

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PIRADS v2, ACR

Use of MRI to guide biopsies

“Cognitive fusion”

In gantry biopsy

MRI/US fusion biopsy

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Use of MRI to guide biopsies

“Cognitive fusion” - inaccurate

In gantry biopsy

MRI/US fusion biopsy

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Use of MRI to guide biopsies

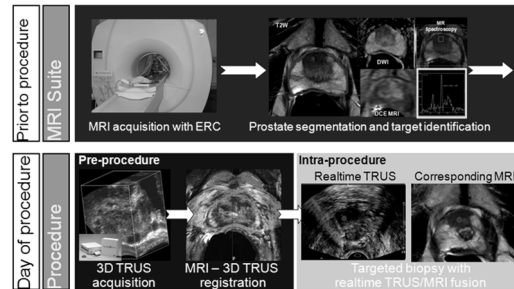
“Cognitive fusion” - inaccurate

In gantry biopsy – resource intensive

MRI/US fusion biopsy



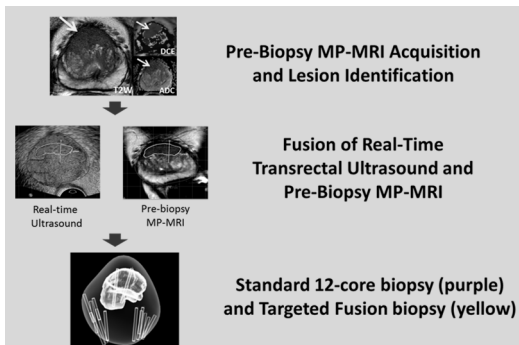
MRI-TRUS Fusion Prostate Biopsies



Spatial Tracking System



Spatial Tracking System



Misconception

MRI does not find small, low-grade lesions that would have otherwise been missed

rather...

MRI/US biopsy detects high grade, high volume disease and misses low grade, low volume “clinically insignificant” disease



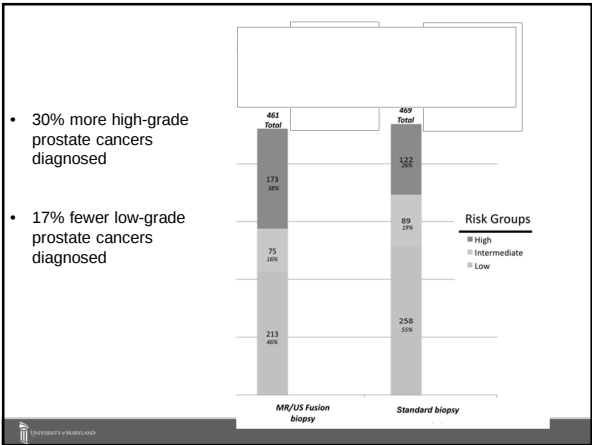
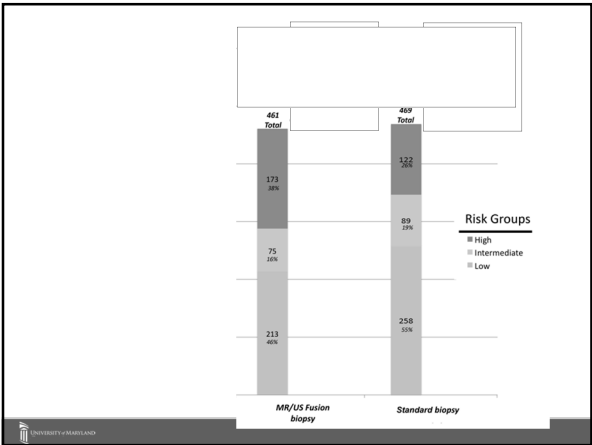
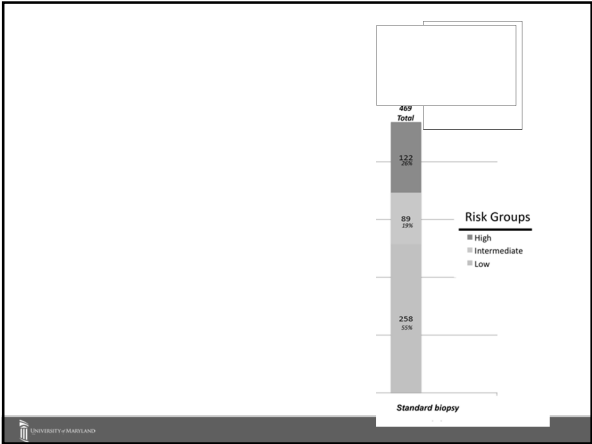
Original Investigation

Comparison of MR/Ultrasound Fusion-Guided Biopsy With Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer

M. Mirhaghi-Siddiqui, MD, Sorush Razi-Bahrani, MD, Boris Turkbey, MD, Arvin K. George, MD, Jason Rothwax, BS, Nabeel Shakir, BS, Chinyerem Okoro, BS, Dima Raskolnikov, BS, Howard L. Parnes, MD, W. Marston Linehan, MD, Maria J. Merino, MD, Richard M. Simon, DSc, Peter L. Choyke, MD, Bradford J. Wood, MD, Peter A. Pinto, MD

jama.comJAMA January 27, 2016 Volume 313, Number 4 399

- Fusion biopsy performed at the NIH from 2007-2014
- Analysis of 1003 men biopsied for suspicion of prostate cancer
- MRI targets on all patients
- Targeted biopsies and standard 12-core biopsies performed on all men



MRI (1215 men)

Visible lesion

12-core standard template biopsy and Targeted MR/US fusion biopsy (1003 men)

Men who opted for radical prostatectomy for treatment

Radical prostatectomy (170 men)

Table 2. Performance of Different Biopsy Approaches in the Detection of Intermediate- to High-Risk Prostate Cancer on Whole-Gland Prostatectomy Specimen

	Targeted MR/Ultrasound Fusion Biopsy	Standard Extended-Sextant Biopsy	Combined Biopsy
Sensitivity, % (95% CI)	77 (67-84)	53 (43-63)	85 (76-91)
Specificity, % (95% CI)	68 (57-78)	66 (54-76)	49 (37-60)
Negative predictive value, % (95% CI)	70 (58-80)	53 (43-63)	73 (58-84)
Positive predictive value, % (95% CI)	75 (65-83)	66 (54-76)	67 (58-75)
Accuracy, % (95% CI)	73 (70-76)	59 (55-63)	69 (65-72)
AUC (95% CI)	0.73 (0.66-0.79)	0.59 (0.52-0.67)	0.67 (0.60-0.74)
P value of comparison with targeted MR/ultrasound biopsy		.005	.04

JAMA. 2015;313(4):390-397. doi:10.1001/jama.2014.17942

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P value of comparison with targeted MR/ultrasound biopsy		.005	.04

Targeted biopsy more sensitive and specific than 12-core biopsy for detection of intermediate to high-risk prostate cancer on whole gland pathology

More likely to diagnose intermediate to high-risk disease

Less likely to diagnose low-risk disease

Study Weaknesses

Original Investigation

Comparison of MR/Ultrasound Fusion-Guided Biopsy With
Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer

- Majority of patients had prior-neg prostate biopsy
 - Skews population towards difficult to detect tumors on standard 12-core
- Men with negative MRI were not biopsied on protocol
 - Unable to tell predictive value of negative MRI
- Sensitivity / Specificity derived from prostatectomy sub-cohort
 - Biased population

JAMA January 27, 2015 Volume 313, Number 4 391

PROMIS Study

Strengths

- All men had no history of no prior prostate biopsy
- Saturation biopsy performed on everyone so no bias of prostatectomy cohort
- Men with negative MRI biopsied

Weaknesses

- 1.5 Tesla MRI used
- No targeted biopsy performed

www.thelancet.com Vol 389 February 25, 2017

Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashim U Ahmed*, Ahmed El-Shater Bosaily*, Louise C Brown*, Rhian Gabe, Richard Kaplan, Mahesh K Parmar, Yolanda Collaco-Morales, Katie Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Parker, Mark Emberton, and the PROMIS study group†

- Number of clinically significant tumors diagnosed on transperineal saturation biopsy but missed by MRI or TRUS

		MP-MRI Total = 17	TRUS-biopsy Total = 119
Number (range of maximum cancer core length, mm)	Gleason 3+3	1 (8mm)	7 (6-11mm)
	Gleason 3+4	16 (6-12mm)	99 (6-14mm)
	Gleason 4+3	0	13 (13-16mm)

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- MRI score strongly associated with risk of clinically significant prostate cancer
 - Gleason 4+3
 - High volume Gleason 3+4 or Gleason 3+3

www.thelancet.com Vol 389 February 25, 2017

MRI as part of screening?

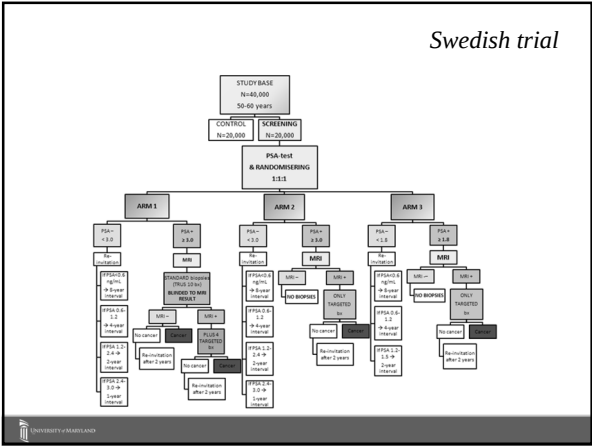
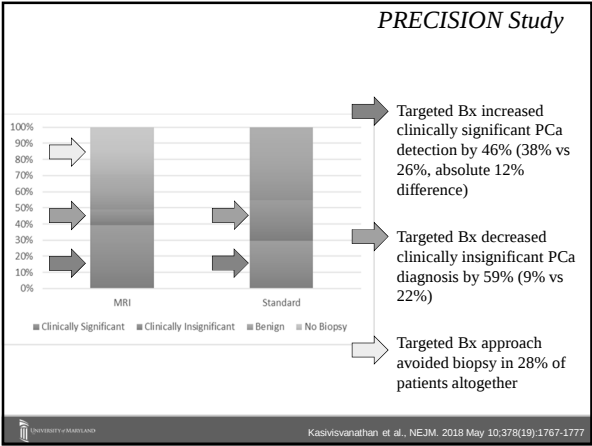
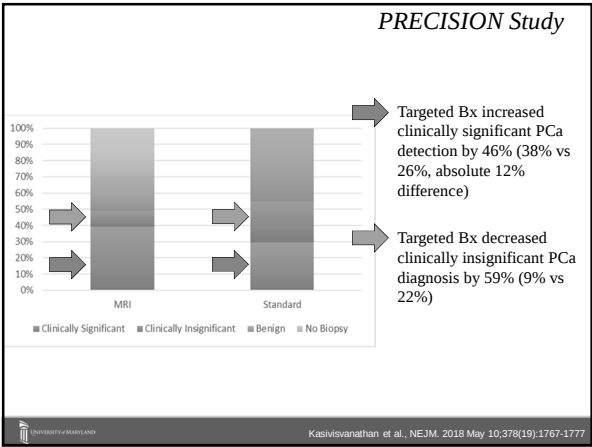
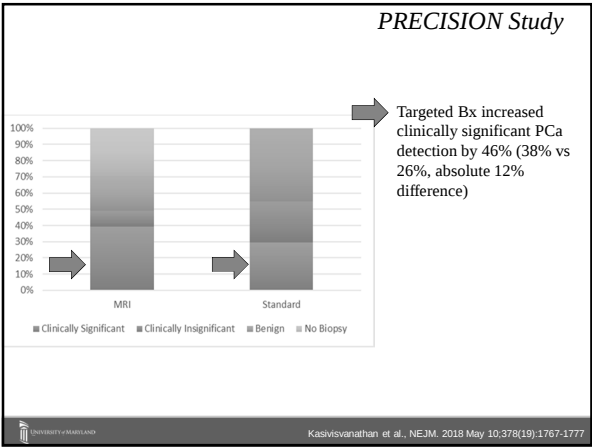
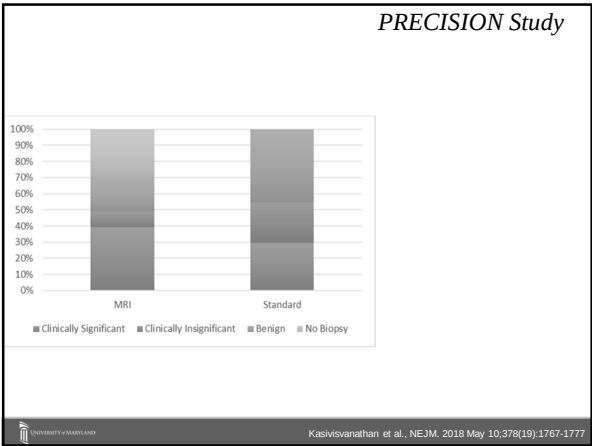
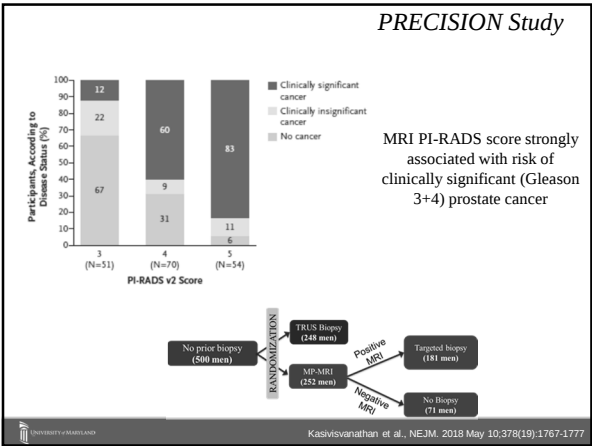
PRECISION Study

The NEW ENGLAND JOURNAL of MEDICINE

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasisvianathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budiau, G. Hellawell, R.G. Hindley, M.J. Roobol, S. Eggener, M. Ghei, A. Villers, F. Bladou, G.M. Villeirs, J. Virdi, S. Boxler, G. Robert, P.B. Singh, W. Venderink, B.A. Hadaschik, A. Ruffon, J.C. Hu, D. Margolis, S. Crouzet, L. Klotz, S.S. Taneja, P. Pinto, I. Gill, C. Allen, F. Giganti, A. Freeman, S. Morris, S. Punwani, N.R. Williams, C. Breen-Graves, J. Deeks, Y. Takewings, M. Emberton, and C.M. Moore, for the PRECISION Study Group Collaborators*

Kasisvianathan et al., NEJM. 2018 May 10;378(19):1767-1777



MRI as part of screening?

Could a 2-step process of PSA, MRI, and then biopsy of only MRI suspicious lesions become a new paradigm for prostate cancer screening?

Pros	Cons
84% decrease in missed diagnosis of Gleason $\geq 4+3$ tumors 27% decrease in the diagnosis of low risk Gleason 3+3 tumors 66% fewer biopsies	- Cost!!! - Infrastructure (MRI still precious utility) - Experience base at medical centers and in community

Active Surveillance

- Demonstrated to be safe, effective method to manage prostate cancer in properly selected men
- Involves regular follow-up with PSA, DRE and repeat prostate biopsy
- 15-40% rate of progression to definitive treatment
 - Unclear how much of “progression” due to previously undiagnosed higher risk tumor vs true progression of tumor from low to higher risk

MP-MRI to follow men in AS

Can MRI be incorporated into how we risk stratify men with prostate cancer?

- NYU cohort of 75 men with negative MP-MRI
- NPV for all PCa 81%, for GS ≥ 7 is 98.7%

Entire cohort	
Overall cancer detection rate on 12-core systematic biopsy, n/N (%)	14/75 (18.7)
Detection of GS ≥ 6 prostate cancer, n/N (%)	13/75 (17.3)
Detection of GS ≥ 7 prostate cancer, n/N (%)	1/75 (1.3)
NPV for all prostate cancer, %	81.3
NPV for GS ≥ 7 prostate cancer, %	98.7

GS, Gleason score; NPV, negative predictive value.

Value Of A Negative MRI

Negative Multiparametric Magnetic Resonance Imaging of the Prostate Predicts Absence of Clinically Significant Prostate Cancer on 12-Core Template Prostate Biopsy

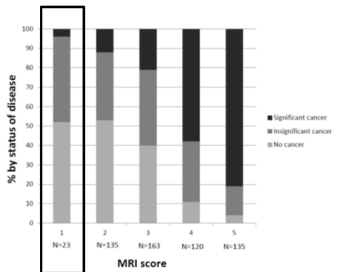
Amanda J. Lu, Jamil S. Syed, Kevin A. Nguyen, Cayce B. Ramef, James Rosoff, Michael Spektor, Angelique Levi, Peter A. Humphrey, Jeffrey C. Walworth, Peter G. Schum, and Preston C. Sprenkle



	Entire Cohort (N = 100)	Biopsy-naïve (N = 38)
Overall cancer detection rate	27/100 (27%)	10/38 (26.3%)
Detection of GS ≥ 6 cancer	24/100 (24%)	9/38 (23.7%)
Detection of GS ≥ 7 cancer	3/100 (3%)	1/38 (2.6%)
NPV of all prostate cancer	73%	73.7%
NPV of GS ≥ 7 prostate cancer	97%	97.4%

Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashem U Ahmed¹, Ahmed El Shater Bosaily¹, Louise C Brown¹, Rhian Gabe, Richard Kiplan, Mahesh K Parmar, Yolanda Collaco-Morales, Einar Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Peake, Mark Emberton, and the PROMIS study group¹



96% Negative Predictive Value for clinically significant prostate cancer for negative MRI

MP-MRI to follow men in AS

Can MRI be used to follow men on AS without biopsy?

- NIH cohort of 58 men who underwent at least 2 serial MRI while on active surveillance
- MRI progression defined as increased:
 - Maximal lesion diameter
 - Number of lesions
 - Maximal lesion suspicion score

Gleason score increase	No MRI progression	MRI progression	Total
No	33	8	41
Yes, detected by	8	9	17

MP-MRI to follow men in AS

- NIH series: Poor performance of MRI progression to predict pathologic progression (53% sensitivity)
- UCLA series: 49 men, more stringent definition of MRI progression, similarly poor association of MRI progression to predict pathologic progression (37% sensitivity)
- Although MRI may be predictive of intermediate/high risk prostate cancer, changes in MRI may not be as sensitive to progression

Felker ER, et al. Serial Magnetic Resonance Imaging in Active Surveillance of Prostate Cancer: Incremental Value. *Eur J Urol*. 195(1421-1427) May 2016

Walton-Olazar A, et al. Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance. *Urologic Oncology*. 23(2015)

Provocative questions for MRI and active surveillance

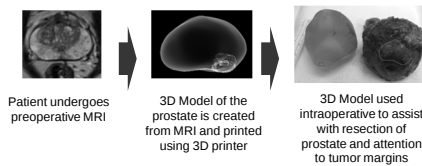
Can MRI be incorporated into how we risk stratify men with prostate cancer?

Yes

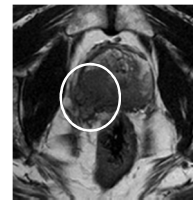
Can MRI be used to follow men on AS without biopsy?

No!

3D printing to assist surgical planning



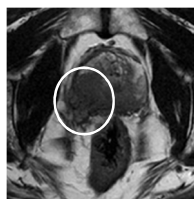
Guidance for radical prostatectomy



- Retrospective case-control study of 134 men with MRI, 134 without, who underwent RARP
- Positive margin rate with MRI = 7.5%
- Positive margin rate no MRI = 18.7%, $p=0.01$
- Multivariate analysis controlling for Gleason score, surgeon, nerve sparing, age, PSA and stage shows MRI still significantly reduces positive margin rate

Petrakis G, Muel G, Pathani AP, et al. Robot-assisted Radical Prostatectomy: Multiparametric MRI Imaging-directed Intraoperative Frozen-Section Analysis to Reduce the Rate of Positive Surgical Margins. *Radiology*. Sept 29, 2014.

Extracapsular extension



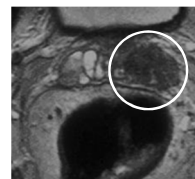
- Retrospective review of 169 men who had radical prostatectomy and preop MRI
- Extracapsular extension seen in 53 (23%)

Performance of MRI for detecting ECE

Sensitivity	48.7%
Specificity	73.9%
Positive Predictive Value	35.9%
Negative Predictive Value	82.8%

Raschke D et al. The Role of Magnetic Resonance Image Guided Prostate Biopsy in Stratifying Men for Risk of Extracapsular Extension at Radical Prostatectomy. *J Urol*. Jul 2015. 194(1):105-111.

Seminal Vesicle Invasion



- Review of 822 men with MRI and targeted MR/US fusion biopsy
- 25 had concern for SV invasion on MRI
- 6 had concern for bilateral SV invasion
- 31 SV's sampled on biopsy, 20 (65%) were positive

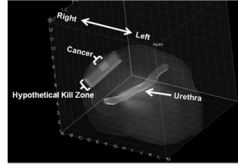
Raschke D et al. Multiparametric magnetic resonance imaging and image-guided biopsy to detect seminal vesicle invasion by prostate cancer. *J Endourol*. Nov 2014. 28(11):1263-1269.

MRI-guided focal prostate cancer therapy?

20% of prostate cancer is unifocal

MRI with MR/US fusion biopsy
gives greater confidence in
distribution of tumor

Some patients with low risk
disease are unable to reliably
follow-up or are uninterested in
active surveillance



Take away points

- MRI can detect regions of concern for prostate cancer
- MRI/US fusion guided biopsies more reliably can sample the prostate for detection of significant cancer
- The role of MRI guided treatment has promise but needs further development

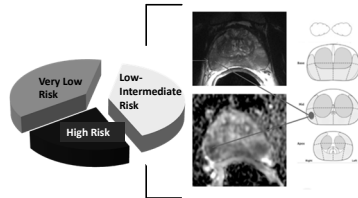
Focal Therapy in Prostate Cancer: a novel approach in select patients

Behfar Ehdaie, MD, MPH

Department of Surgery,
Urology Service

Department of Epidemiology
and Biostatistics

Memorial Sloan Kettering
Cancer Center



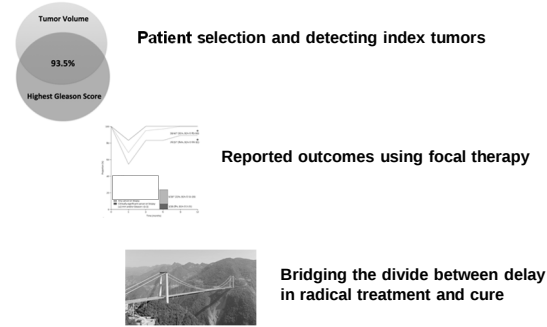
[Hoffman, 2014]

Disclosures

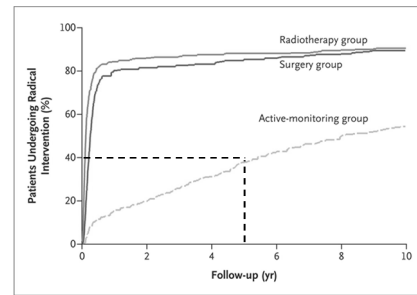
P.I. Multicenter Clinical Trial (no salary support), InSightec
Medical Advisory Board Speaker, Myriad Genetics
Reports no relationships with a commercial interest



This talk will outline the role of focal therapy as a viable treatment for localized prostate cancer

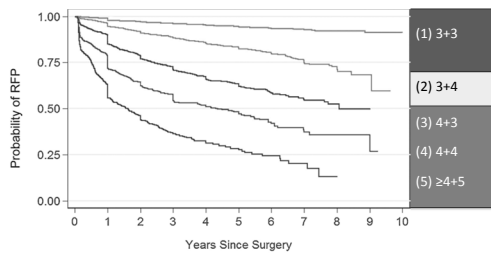


Approximately 40% of men randomized to active monitoring underwent radical treatment within 5 years



[Hamdy, 2016]

Biopsy pathology primary Gleason grade is prognostic of disease recurrence after treatment



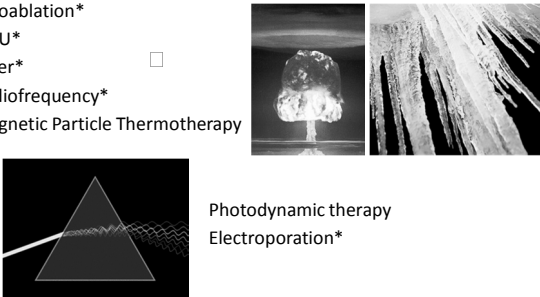
[Epstein, 2016]

Therefore, focal therapy or *partial gland ablation* is a potentially effective treatment with minimal morbidity that delays radical treatment for men with intermediate risk prostate cancer



Energy-based technology for ablation of tissue vary by thermal or non-thermal therapies

Cryoablation*
HIFU*
Laser*
Radiofrequency*
Magnetic Particle Thermotherapy
Photodynamic therapy
Electroporation*

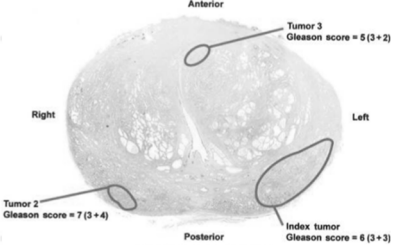


Tumor localization within prostate glandular anatomy informs patient and treatment selection

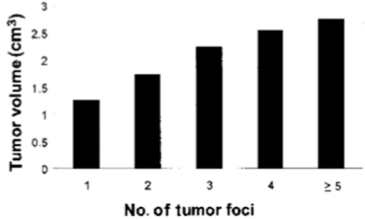


[Ahmed, 2012]

Click to



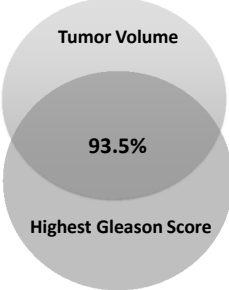
Click to



No. of tumor foci	Tumor volume (cm³)
1	~1.2
2	~1.7
3	~2.2
4	~2.5
≥ 5	~2.8



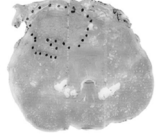
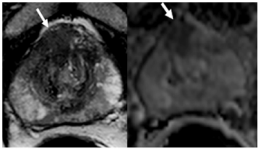
Adverse pathologic features, including highest stage, Gleason score, and tumor volume often concur in the same *index* lesion



[Arora, 2004]

The sensitivity of MRI to detect prostate cancer is improved with larger tumor volumes and higher Gleason scores

Overall PPV: 98%
Sensitivity:
Gleason ≥ 7 : 0.69-0.80 ($p < 0.05$)
 < 7 : 0.27-0.47
Volume $> 5\text{mm}$: 0.53-0.68 ($p < 0.05$)
 $\leq 5\text{mm}$: 0.13-0.37



[Turkbey, 2012]

MR-targeted biopsy accurately detects the location and identifies the Gleason score of the index tumor

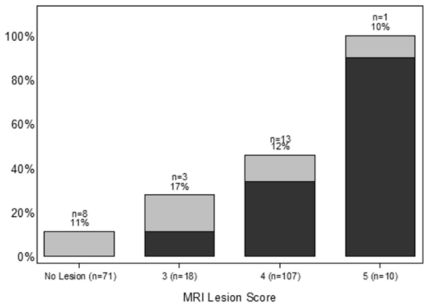
Index tumor *location* accurately detected: 95% of cases (128/135)
Gleason score identified: 69.5% of cases (89/128)

MR-targeted biopsy	Radical Prostatectomy		
	Gleason 6	Gleason 7	Gleason ≥8
Gleason 6	23 (70%)	10 (30%)	0
Gleason 7	2 (4%)	50 (88%)	5 (8%)
Gleason ≥8	0	6 (30%)	14 (70%)



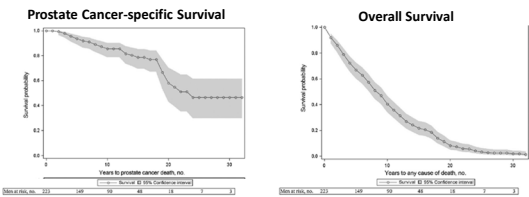
[Baco, 2015]

Gleason score ≥7 prostate cancer detected by MRI-targeted biopsy (black bar) compared to detection by standard 14-core biopsy only (gray bar)



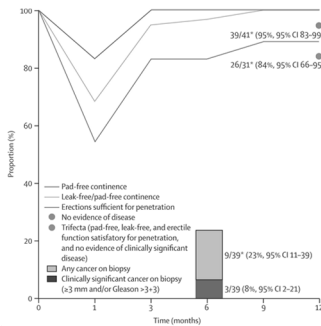
[Ehdaie, 2016]

Surrogate oncologic outcomes are essential to study the benefit of focal therapy to patients



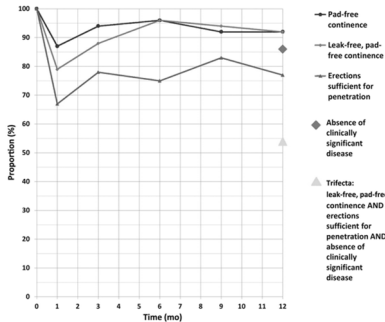
[Popiolek, 2013]

Focal therapy of uni- and multifocal prostate cancer leads to a low-rate of genito-urinary functional impairment with effective early absence of cancer



[Ahmed, 2012]

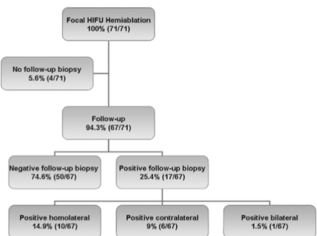
Focal therapy of index tumors has low rates of genitourinary side effects and acceptable short-term absence of clinically significant cancer



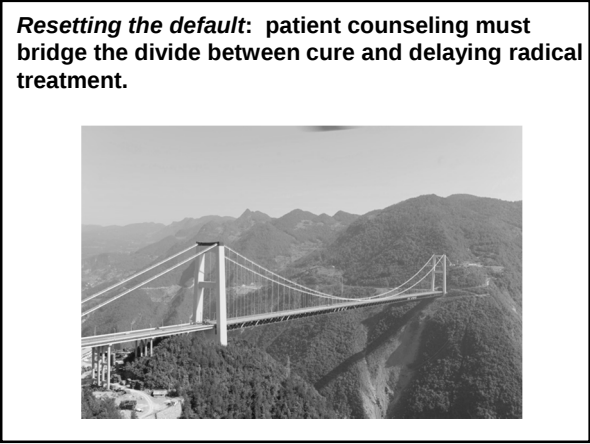
[Ahmed, 2015]

Focal High-intensity Focused Ultrasound Targeted Hemiblation for Unilateral Prostate Cancer: A Prospective Evaluation of Oncologic and Functional Outcomes

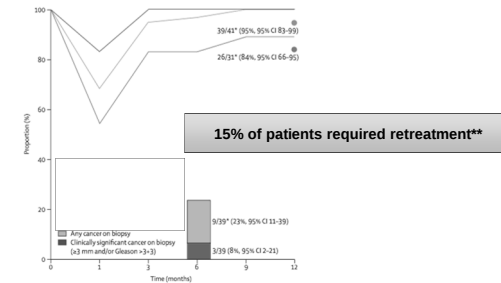
Ernesto R. Cordeiro Feijoo, Arjun Sivaraman, Eric Barret*, Rafael Sanchez-Salas, Marc Galliano, Francois Rozet, Dominique Praprotnick, Nathalie Cathala, Annick Mombet, Xavier Cathelineau



[Feijoo, 2015]

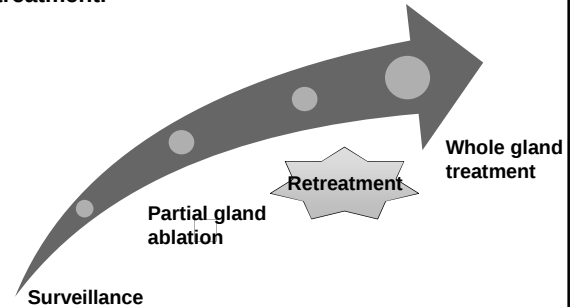


Retreatment is not uncommon after focal therapy



[Ahmed, 2012]

Patients should be informed that retreatment of the area of focal treatment is expected within the spectrum of management to delay radical treatment.



Focal therapy for prostate cancer is safe and has favorable functional outcomes

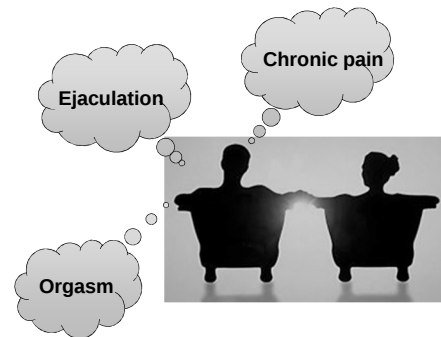
Platinum Priority – Collaborative Review – Prostate Cancer
Editorial by SII on pp. x-y of this issue

New and Established Technology in Focal Ablation of the Prostate:
A Systematic Review

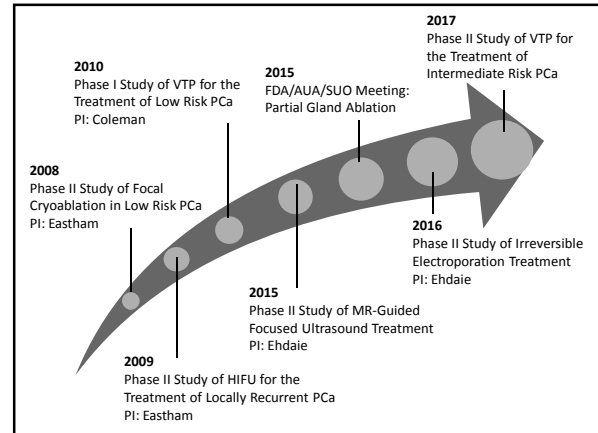
Massimo Valicelli^{a,b,c}, Yusef G. Ghanem^a, Scott E. Egge^a, Herbert Lepor^a,
Thomas J. Pisansky^d, Arnold Villers^e, Mark Emberton^a

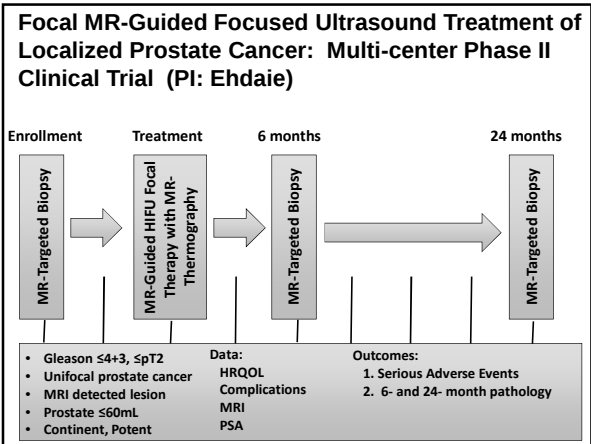
- Systematic review: 14 studies
- Potency preservation (%): 76.9% - 100%
- Leak free (%): 90-100%
- Serious adverse events (%): 0% - 4.2%

However, is sexual function *only* potency for patients undergoing focal therapy?



Patient preferences regarding sexual function expectations should be elicited and discussion of outcomes must be expanded to sexual satisfaction





In conclusion, focal therapy of index tumors provides an alternative treatment for intermediate risk prostate cancer

Intervention Cohort

- Treatment of the index tumor and subsequent surveillance of low risk tumors overcomes challenges in multifocal cancer
- The goals of focal therapy should be separate from whole gland treatment

The MRI scan shows a cross-section of the prostate with a focal lesion outlined in a white box. Technical details visible on the scan include: TR: 12.00, TE: 18.11, MAG: 180.0, and a 60mm scale bar.

Thank You

Prostate Cancer: Surgical Management



Gerald L. Andriole, MD
Robert K. Royce Distinguished Professor
Chief of Urologic Surgery
Siteman Cancer Center
Barnes-Jewish Hospital
Washington University School of Medicine
St. Louis, Missouri

Disclosures

- Clinical Investigator:
 - Nanospectra, FKD Therapies, Pfizer
- Consultant/Advisor:
 - Augmenix, 3D Biopsy, Stratify Genomics, Janssen, Astellas, Blue Earth Diagnostics Inc.
- Research Support:
 - National Cancer Institute
 - NIH-NIDDK
 - Peter Michael Foundation
 - St. Louis Men's Group Against Cancer
 - Barnes-Jewish Hospital Foundation
 - Mid-West Stone Institute

Surgical Treatment of Prostate Cancer: Outline of talk

- Evidence that it works
- Patient Selection
- Tumor Factors
- Pelvic Lymphadenectomy
- Radical Prostatectomy
 - Open
 - Perineal
 - Laparoscopic $\pm$ Robotic Assistance

Surgical Treatment of Prostate Cancer: Outline of talk

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Randomized Trials of Radical Prostatectomy

- SPG-4: Pre-PSA era
- PIVOT: Early PSA screening era
- PROTECT: Contemporary PSA screening

THE NEW ENGLAND JOURNAL OF MEDICINE

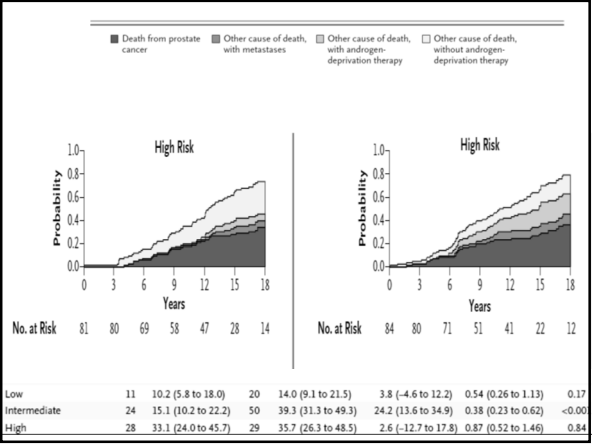
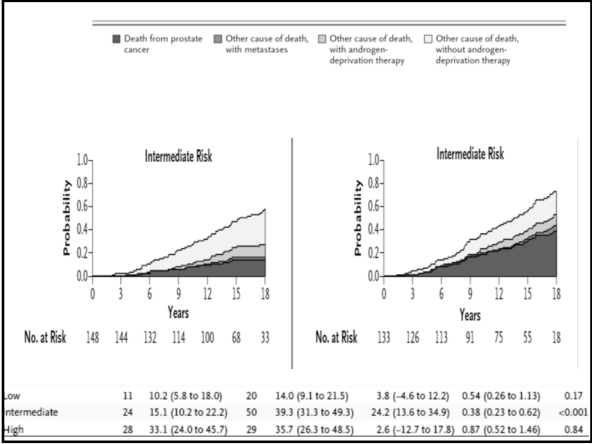
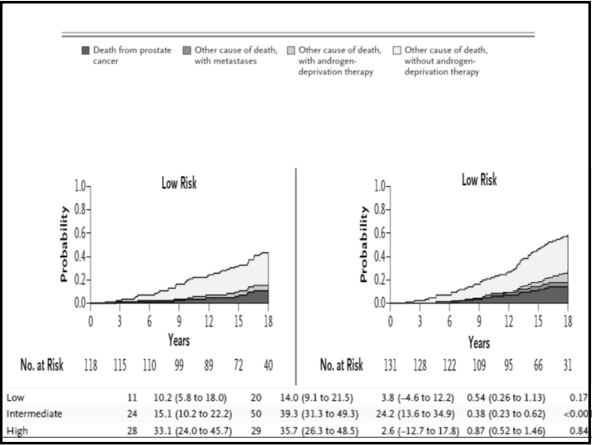
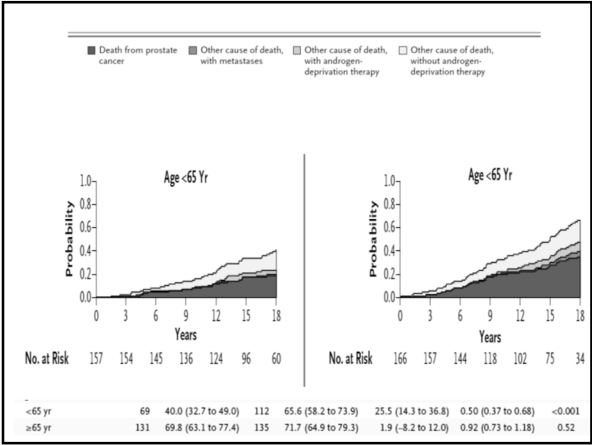
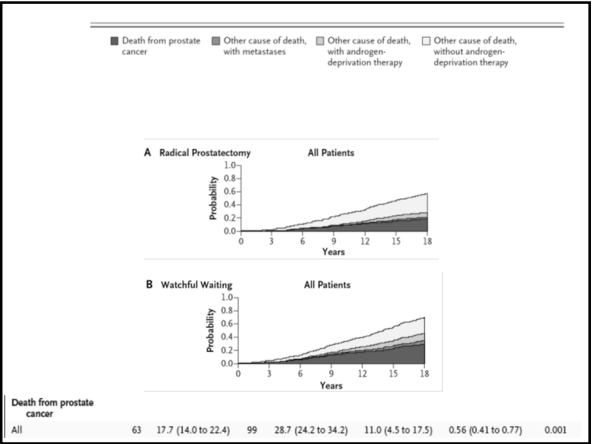
ORIGINAL ARTICLE

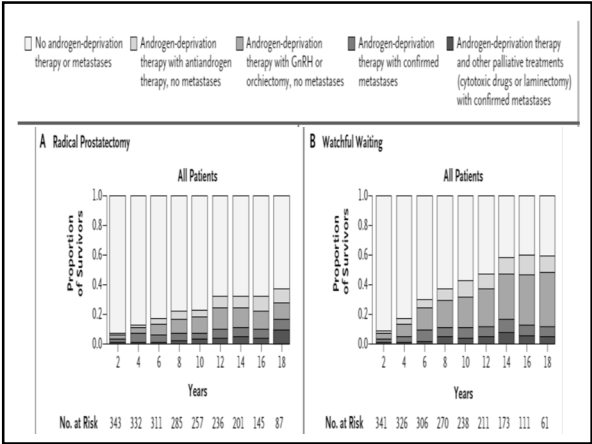
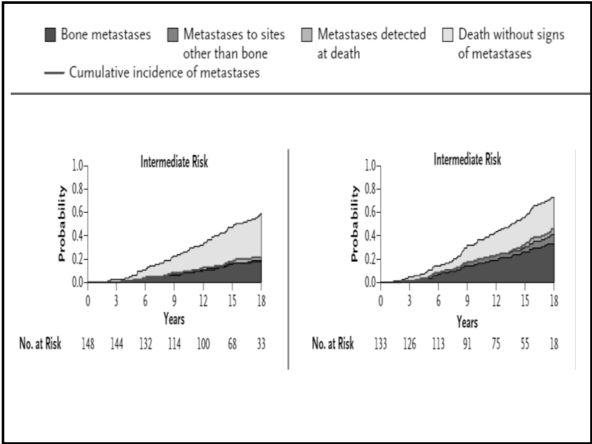
Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

Anna Bill-Awelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Rider, Sc.D., Kimmo Taaari, M.D., Ph.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Sven-Olof Andersson, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Ove Andrén, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.

N ENGL J MED 370;10 NEJM.ORG MARCH 6, 2014

End Point	Cumulative Incidence				Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radical Prostatectomy (N=347)		Watchful Waiting (N=348)				
	no. of events	% (95% CI)	no. of events	% (95% CI)			
Death from any cause					percentage points (95% CI)		
All	200	56.1 (50.9 to 62.0)	247	68.9 (63.8 to 74.3)	12.7 (5.1 to 20.3)	0.71 (0.59 to 0.86)	<0.001
Age							
<65 yr	69	40.0 (32.7 to 49.0)	112	65.6 (58.2 to 73.9)	25.5 (14.3 to 36.8)	0.50 (0.37 to 0.68)	<0.001
≥65 yr	131	69.8 (63.1 to 77.4)	135	71.7 (64.9 to 79.3)	1.9 (-8.2 to 12.0)	0.92 (0.73 to 1.18)	0.52
Tumor risk							
Low	51	43.4 (34.8 to 54.1)	85	59.1 (50.7 to 68.8)	15.6 (2.5 to 28.8)	0.57 (0.40 to 0.81)	0.002
Intermediate	87	57.1 (49.0 to 66.4)	95	72.5 (64.5 to 81.6)	15.5 (3.3 to 27.6)	0.71 (0.53 to 0.95)	0.02
High	62	73.3 (63.8 to 84.2)	67	78.8 (69.7 to 89.2)	5.6 (-8.5 to 19.6)	0.84 (0.60 to 1.19)	0.34
Death from prostate cancer							
All	63	17.7 (14.0 to 22.4)	99	28.7 (24.2 to 34.2)	11.0 (4.5 to 17.5)	0.56 (0.41 to 0.77)	0.001
Age							
<65 yr	31	18.3 (13.1 to 25.7)	58	34.1 (27.3 to 42.5)	15.8 (6.0 to 25.5)	0.45 (0.29 to 0.69)	0.002
≥65 yr	32	17.3 (12.5 to 24.0)	41	23.9 (18.2 to 31.5)	6.6 (-2.1 to 15.2)	0.75 (0.47 to 1.19)	0.19
Tumor risk							
Low	11	10.2 (5.8 to 18.0)	20	14.0 (9.1 to 21.5)	3.8 (-4.6 to 12.2)	0.54 (0.26 to 1.13)	0.17
Intermediate	24	15.1 (10.2 to 22.2)	50	39.3 (31.3 to 49.3)	24.2 (13.6 to 34.9)	0.38 (0.23 to 0.62)	<0.001
High	28	33.1 (24.0 to 45.7)	29	35.7 (26.3 to 48.5)	2.6 (-12.7 to 17.8)	0.87 (0.52 to 1.46)	0.84





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 19, 2012 VOL. 367 NO. 3

Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D., William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D., Patricia Gibsby, M.D., B. Mayer Grob, M.D., Imad Nosouli, M.D., Padirini Iyer, M.D., Ruben Cartagena, M.D., Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Roohollah Sharifi, M.D., William Blank, M.D., Parikshit Pandya, M.D., Gerald L. Andriole, M.D., Daniel Culpin, M.D., and Thomas Wheeler, M.D., for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group

N Engl J Med 2012;367:203-13.
DOI: 10.1056/NEJMoa1113162
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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Karen M. Jones, M.S., Michael J. Barry, M.D., Gerald L. Andriole, M.D., Daniel Culpin, M.D., Thomas Wheeler, M.D., William J. Aronson, M.D., and Michael K. Brawer, M.D.

N ENGL J MED 377;2 NEJM.ORG JULY 13, 2017

PIVOT Objective

Among men with screen-detected, clinically localized prostate cancer during the “early” PSA era, does the intent to treat with radical prostatectomy reduce all-cause &/or prostate cancer mortality compared to observation?

Inclusion Criteria

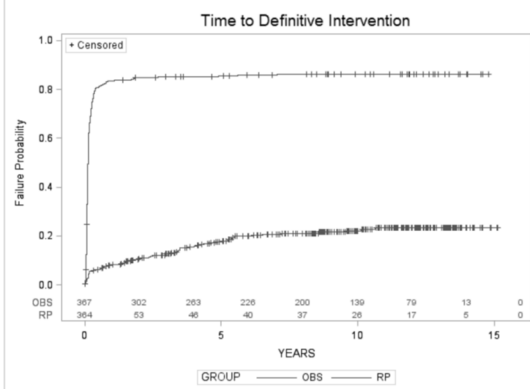
- Age ≤ 75 years
- T1-2, NX, M0 (all histologic grades)
- PSA < 50 ng/mL
- Diagnosed ≤ 12 months
- Radical Prostatectomy candidate
 - Predicted life expectancy > 10 years

Endpoints

- **Primary endpoint**
 - All-cause mortality
- **Secondary endpoint**
 - CaP mortality

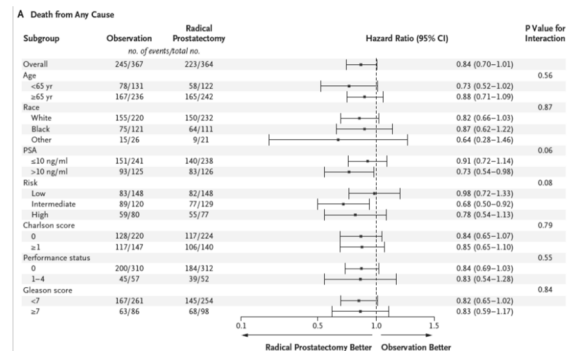
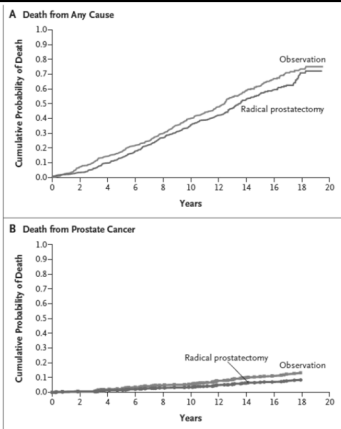
Tumor Characteristics

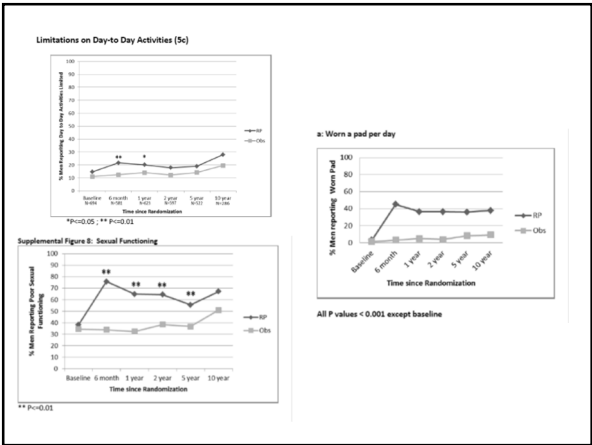
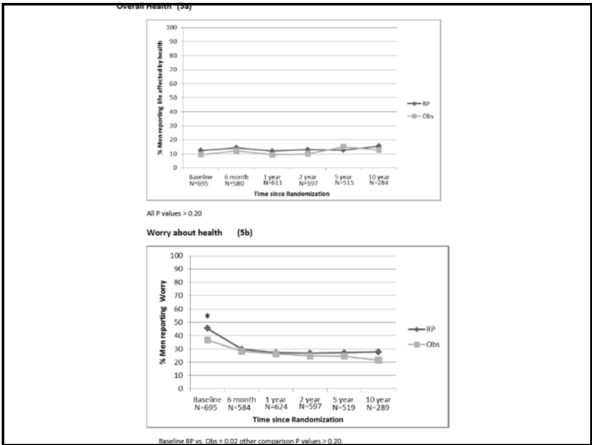
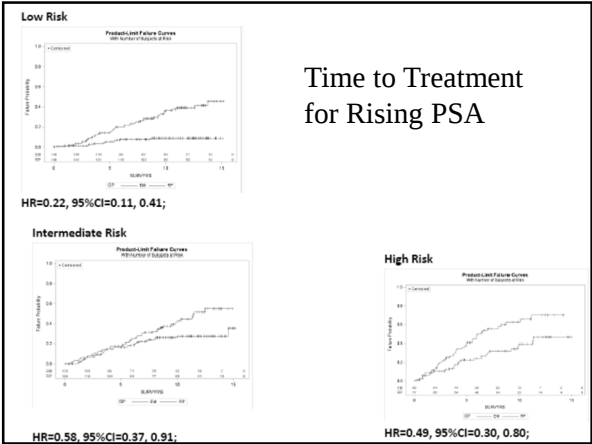
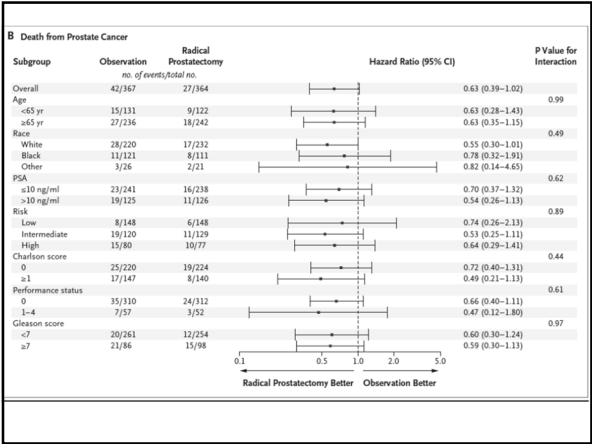
Characteristic	Observation	RP
• PSA Mean (median)	10.2 (7.8)	10.1 (7.8)
– < 4.0 (%)	10.9	11.5
– ≥ 20 (%)	10.1	10.4
• Stage: T1c (%)	49.9	50.8
• Gleason Score (%)		
≤6	70.1	69.8
7	17.4	19.0
8-10	6.0	8.0
• D'Amico Tumor Risk		
Low	40.3	40.7
Intermediate	32.7	35.4
High	21.8	21.2



Follow-up & Cumulative Events

- **Median follow-up**
 - 12.7 years (IQ range 12 to 19.5 years)
- **All-cause mortality**
 - 468/731 (64.1%)
 - Higher than expected
- **Prostate cancer mortality**
 - 69/731 (9.4%)





Criticisms of PIVOT

- Volunteers were sicker than most RP series
 - Higher death rate than anticipated
- Underpowered
 - Designed for 2000 patients
 - Need ~1500 pts. for 80% power
- Crossover/Non-compliance further dilutes power
 - ~20% in each arm

	PIVOT	SPG-4
F-up (yr)	19.5	23.2
Death (%)	64	64
CaP Death (%)	9.4	29

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oakey, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

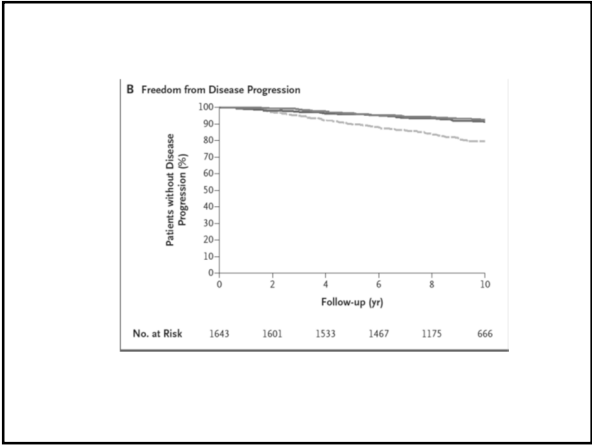
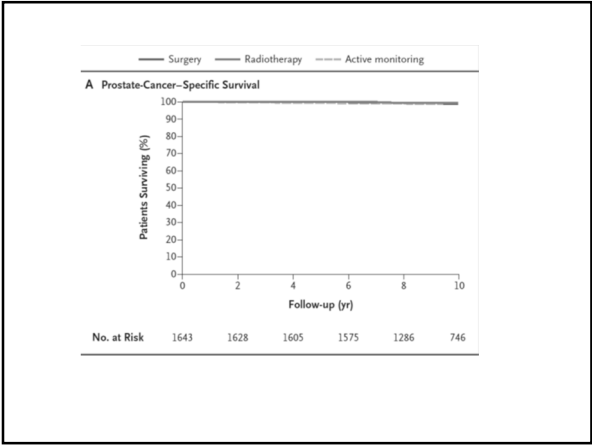
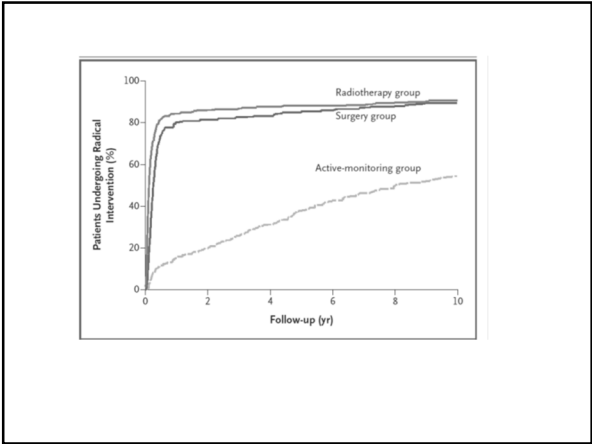


Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.				
Variable	Active Monitoring (N=345)	Surgery (N=533)	Radiotherapy (N=545)	P Value ^a
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer ^b	8	5	4	
Prostate-cancer-specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004

	SPG-4	PIVOT	Klotz	PROTECT
Years	1989–1999	1994–2002	1995–	1999–2009
Intervention	RP v WW	RP v Obs	AS	RP or XRT v AS
# Biopsy cores	????	6	???	10
# Randomized	695 (Unk)	731 (15%)	???	1643 (62%)
Age (mean)	<75 (65)	<75 (67)	<90 (68)	50–69 (61)
% White	???	62	???	99
Mean PSA	13	10	5.2	5.8
Clin T1c	11	50	78	76
Gleason <7	60	74	84	77

- Evidence that it works
- Patient Selection
- Tumor Factors
- Pelvic Lymphadenectomy
- Radical Prostatectomy
 - Open
 - Perineal
 - Laparoscopic + Robotic Assistance

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Comprehensive
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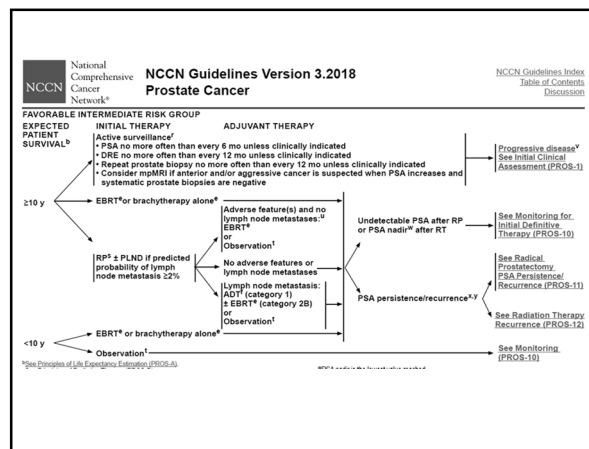
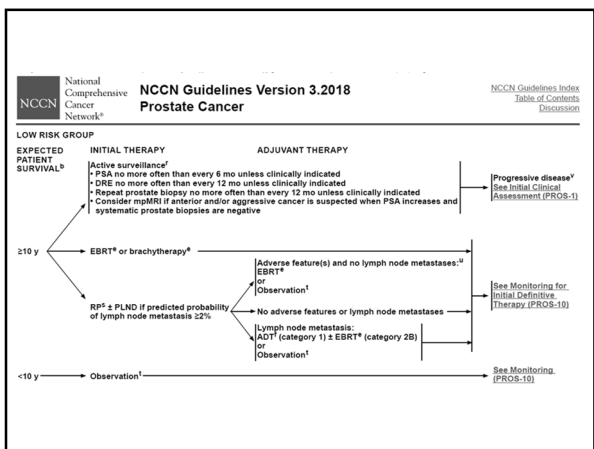
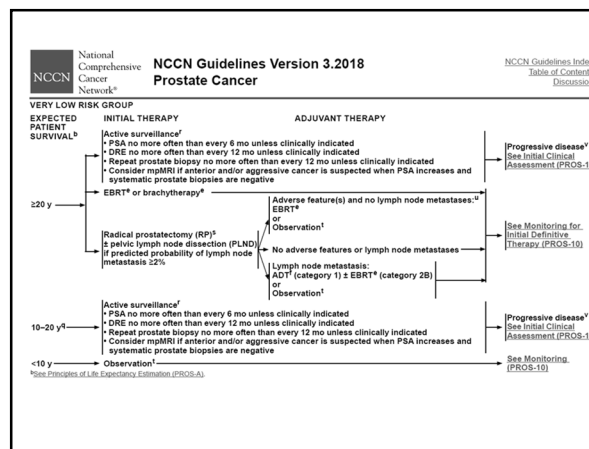
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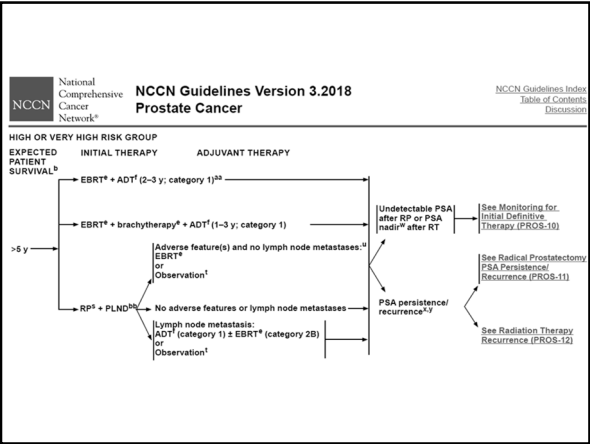
Prostate Cancer

NCCN Guidelines Index
[Table of Contents](#)
[Discussion](#)

PRINCIPLES OF LIFE EXPECTANCY ESTIMATION

- Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment.
- Estimation of life expectancy is possible for groups of men but challenging for individuals.
- Life expectancy can be estimated using the Social Security Administration tables (www.ssa.gov/OACT/STAT/tables4c6.html) or the WHO's Life Tables by country (<http://apps.who.int/ghodata/view/main.60009?lang=en>).
- Life expectancy can then be adjusted using the clinician's assessment of overall health as follows:
 - Best quartile of health - add 50%
 - Worst quartile of health - subtract 50%
 - Middle two quartiles of health - no adjustment
- Example of 8-year increments of age are reproduced in the *NCCN Guidelines for Older Adult Oncology* for life expectancy estimation.





Predicting Life Expectancy

- Challenging
- Over-estimates more common than under-estimate
- Need better tools

Surgical Treatment of Prostate Cancer: Outline of talk

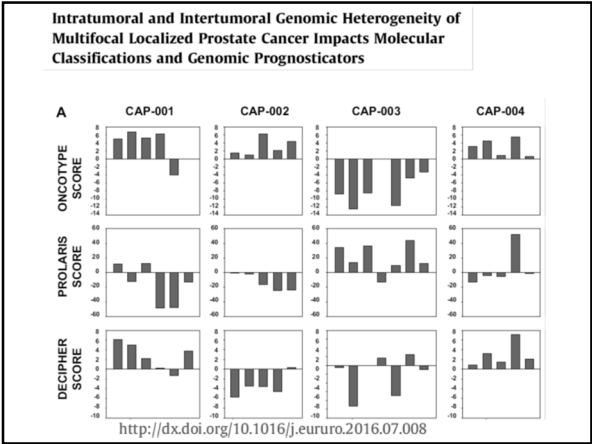
- Evidence that it works
- Patient Selection
- Tumor Factors
- Pelvic Lymphadenectomy
- Radical Prostatectomy
 - Open
 - Perineal
 - Laparoscopic ± Robotic Assistance

NCCN Guidelines Version 3.2018 Prostate Cancer					
RISK STRATIFICATION AND STAGING WORKUP					
Risk group	Clinical/pathologic features	Imaging ²	Molecular testing of tumor	Germline testing	Initial therapy ³
Very low ⁴	• T1c AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL AND • Fewer than 5 positive biopsy fragments positive, ≤50% cancer in each fragment (core) AND • PSA density <0.15 ng/mL/g	Not indicated	Not indicated	Consider if strong family history ⁵	See PROS-4
Low ⁴	• T1-T2a AND • Gleason score ≤6/grade group 1 AND • PSA <10 ng/mL AND • Percentage of positive biopsy cores <50%	Not indicated	Consider if life expectancy >10y ⁶	Consider if strong family history ⁵	See PROS-5
Favorable intermediate ⁴	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 OR Gleason score 3 OR • PSA 10-20 ng/mL AND • Percentage of positive biopsy cores <50%	• Bone imaging ² not recommended for staging • Pelvic a abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Consider if life expectancy >10y ⁶	Consider if strong family history ⁵	See PROS-6
Unfavorable intermediate ⁴	• T2b-T2c OR • Gleason score 3+4=7/grade group 2 or Gleason score 4-5/grade group 3 OR • PSA 10-20 ng/mL	• Bone imaging ² recommended if T2 and PSA >10 ng/mL • Pelvic a abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider if strong family history ⁵	See PROS-7
High ⁴	• T3a OR • Gleason score ≥8/grade group 4 or Gleason score ≥7-8/grade group 5 OR • PSA >20 ng/mL	• Bone imaging ² recommended • Pelvic a abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider ⁵	See PROS-8
Very high ⁴	• T3b-T4 OR • Primary Gleason pattern 5 OR • ≥4 cores with Gleason score 5-10/grade group 4 or 5	• Bone imaging ² recommended • Pelvic a abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not routinely recommended	Consider ⁵	See PROS-8
Regional ⁴	Any T, N1, M0	Already performed	Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR) ⁷	Consider ⁵	See PROS-9
Metastatic ⁴	Any T, Any N, M1	Already performed	Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR ⁷	Consider ⁵	See PROS-13

NCCN Guidelines Version 3.2018 Prostate Cancer					
Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis					
Test	Platform	Populations Studied	Outcomes Reported (Test Independent Endpoints)	References	Molecular Diagnostic Services Program (MDSP) Recommendations
Decipher	Whole-transcriptome TAD RNA expression (12,000 genes) algorithmically derived algorithmically derived optimized for FFPE tissue	Post radical prostatectomy (RP) adverse pathologic high-risk features	• Metastasis • Prostate cancer-specific mortality • Postoperative radiation sensitivity (PORTOS)	12,13,18,19,20,21	Cover post-RP for 1) T2 with positive margins, 2) any pT3 disease, 3) rising PSA (alone or with)
		Post RP, biochemical recurrence	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Post RP, adjuvant or salvage radiation	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Biopsy, localized prostate cancer post RP or EBRT	• Metastasis • Prostate cancer-specific mortality • Gleason grade at disease at RP		
KI-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT	• Metastasis	10,101	Not recommended
		Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality		
Decipher Prostate	Quantitative RT-PCR for 12 (4) cell cycle-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	• Non-organ-confined pT3 or Gleason grade 4 disease on RP	12,13,18,19,20,21	Cover post-RP for NCCN very low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prostate	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	• Prostate cancer-specific mortality	12,13,18,19,20,21	Cover post-RP for NCCN very low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
		Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality		
		Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis		
		Biopsy, intermediate-risk treated with EBRT	• Biochemical recurrence		
		RP, node-negative localized prostate cancer	• Biochemical recurrence		
ProMark	Multiple immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	• Non-organ-confined pT3 or Gleason pattern 4 disease on RP	22	Cover post-RP for NCCN very low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
PTEN	Fluorescent in situ hybridization or IHC	TURP, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	10,101	Not recommended
		Biopsy, Gleason grade 3+3	• Upgrading to Gleason pattern 4 on RP		
		RP, high-risk localized disease	• Biochemical recurrence		

Tissue Genomic Markers

- All validated
- All have significant effect on treatment decisions
- Never compared!



Use of Genomic Tests		
Clinical Scenario	Use of Genomic Test	Best Endpoint
Very Low Risk	No (except for youngest pts)	Adverse Pathology; Metastases Risk
Low risk: low volume GI 3 + 3	Selectively based on life expectancy and risk tolerance	
Low risk: high volume GI 3 + 3	Yes	
Intermediate Risk: low volume GI 3+ 4	Yes	Metastasis Risk or Mortality
Intermediate Risk: high volume 3+4 or any 4+ 3	No	
High Risk	No	

Staging of Clinically Localized CaP

- PET imaging (eg, Gallium-PSMA) has shown some promise to identify occult metastases in “high-risk” otherwise localized CaP
 - Suspicious nodes identified in 25% pts (Rad. 288:495, 2018)
- May also identify intraprostatic disease better than multiparametric MRI

Surgical Treatment of Prostate Cancer: Outline of talk

- Evidence that it works
- Patient Selection
- Tumor Factors
- Pelvic Lymphadenectomy
- Radical Prostatectomy
 - Open
 - Perineal
 - Laparoscopic $\pm$ Robotic Assistance

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NCCN Guidelines Index Table of Contents Discussion

PRINCIPLES OF SURGERY

Pelvic Lymph Node Dissection

* An extended PLND will discover metastases approximately twice as often as a limited PLND. Extended PLND provides more complete staging and may cure some men with microscopic metastases; therefore, an extended PLND is preferred when PLND is performed.

* An extended PLND includes removal of all node-bearing tissue from an area bound by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.

* A PLND can be excluded in patients with <2% predicted probability of nodal metastases by nomograms, although some patients with lymph node metastases will be missed.

* PLND can be performed using an open, laparoscopic, or robotic technique.

The 2 % cut-off avoids 48% of the PLNDs and misses 12% of positive nodes.

NCCN favors Kattan nomogram for North American surgeons.

If performing PLND, favor extended dissection; removes more nodes and may have a survival advantage.

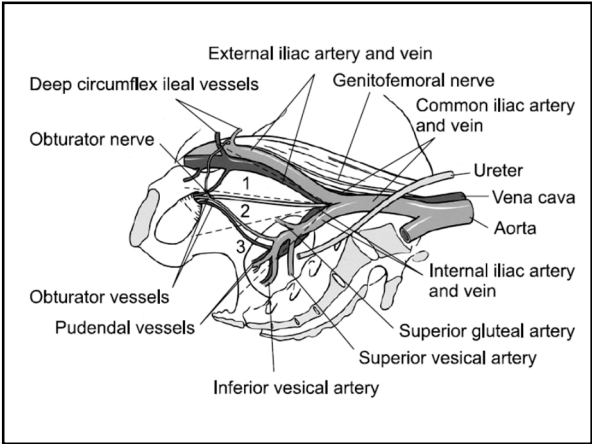


TABLE 1. Nomograms for predicting the lymph node involvement in prostate cancer

Study	No. of patients	Predictors	Extent of PLND	Prevalence of LNI, %	Predictive accuracy, %
Caginanos et al [42]	7,014	PSA, clinical stage, biopsy Gleason score	Limited	3.7	76
Kattan et al [4,10,11,33,51]	697	PSA, clinical stage, biopsy Gleason score	Limited	8	76.5
Makarov et al [12]	5,790	PSA, clinical stage, biopsy Gleason score	Limited	1	88
Briganti et al [13,41,53,55]	602	PSA, clinical stage, biopsy Gleason score	Extended	11	76
Briganti et al [13,41,53,55]	278	PSA, clinical stage, biopsy Gleason score, percentage of positive cores	Extended	10.4	83
Blumstein et al [14]	1,632	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Bischoff et al [43]	481	PSA, clinical stage, biopsy Gleason score	Limited	7.7	NA
Narayan et al [44,45]	932	PSA, biopsy Gleason score	Limited	11	NA
Conrad et al [54,15]	944	No. of positive biopsies, no. of biopsies containing any Gleason grade 4 or 5 cancer	Limited	8.1	NA
Roech et al [45]	212	PSA, biopsy Gleason score	Limited	17	NA
Crawford et al [9,46,47]	4,133	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Battuello et al [46,47]	6,135	PSA, clinical stage, biopsy Gleason score	Limited	4.6	81
Han et al [8,47,48]	5,744	PSA, clinical stage, biopsy Gleason score, age	Limited	5	88
Poulakis et al [49]	201	PSA, clinical biopsy Gleason score, and pelvic coil MRI findings	Limited	10	91
Karam et al [50]	425	PSA, clinical stage, biopsy Gleason score, preoperative plasma endoglin	Limited	3.3	97.5
Wang et al [51]	411	PSA, clinical biopsy Gleason score, and pelvic coil MRI findings	Limited	5	89.2

PLND: pelvic lymph node dissection, LNI: lymph node invasion, PSA: prostate-specific antigen, MRI: magnetic resonance imaging, NA: not available

Pelvic Lymphadenectomy for Prostate Cancer

- Adds some, but minimal, morbidity to RP
- Careful occlusion of lymphatic channels
 - Clips, energy sources
- Post-op drain if extraperitoneal RP; lymphocele may still occur if transperitoneal but is less frequent
- Possible therapeutic benefit to extended template lymphadenectomies

Surgical Treatment of Prostate Cancer: Outline of talk

- Evidence that it works
- Patient Selection
- Tumor Factors
- Pelvic Lymphadenectomy
- Radical Prostatectomy
 - Perineal
 - Open Retropubic “Anatomic”
 - Laparoscopic ± Robotic Assistance

Open Prostatectomy

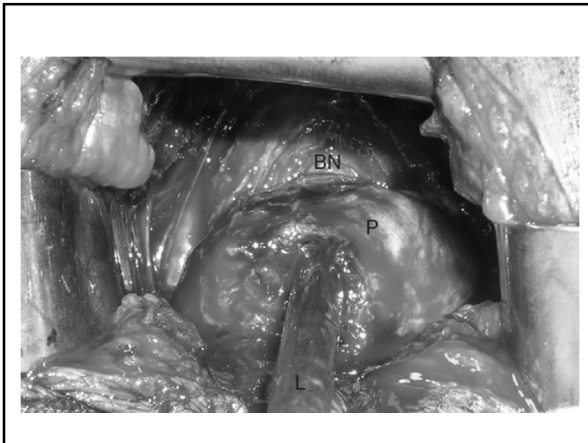
- Gold Standard
- Initially used perineal approach
- More recently, retropubic approach favored.
- Laparoscopic and Robotic-assisted techniques use the same principles of the open, retropubic “anatomic” approach

Perineal Prostatectomy

- Bowel Prep pre-op
- Perform laparoscopic PLND if risk of involved nodes exceeds 2%
- Contraindicated if patient cannot be positioned in exaggerated lithotomy position (eg, ankylosing conditions) or if prostate is large (>100 gm)

Perineal Prostatectomy Positioning





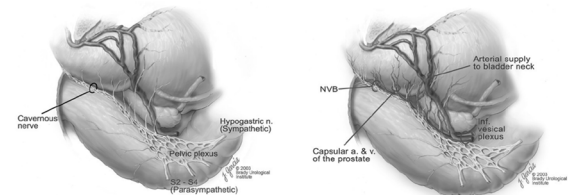
Perineal Prostatectomy Outcomes

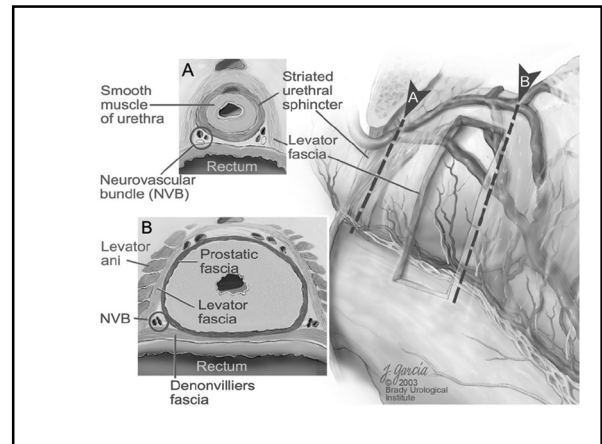
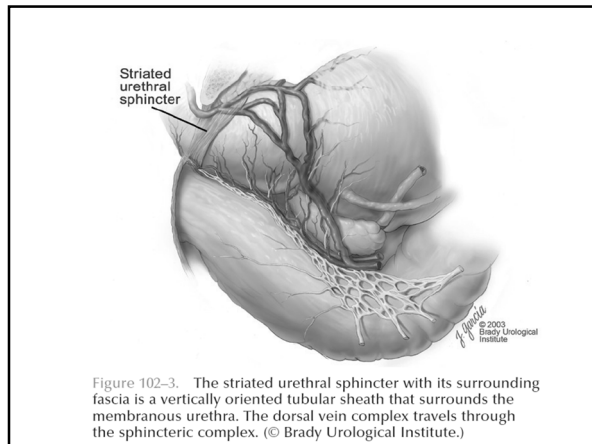
- Similar positive margin and PSA failure rates as other approaches
- In general, shorter operative time
- Neuropraxia rare (<2%)
- Transfusion rate ~ 5%
- Continence rates similar to other approaches
- Potency ranges from 35-70%

Anatomic Prostatectomy

Open Retropubic, Laparoscopic and Robot-Assisted Laparoscopic techniques use the same principles articulated by Walsh et al.

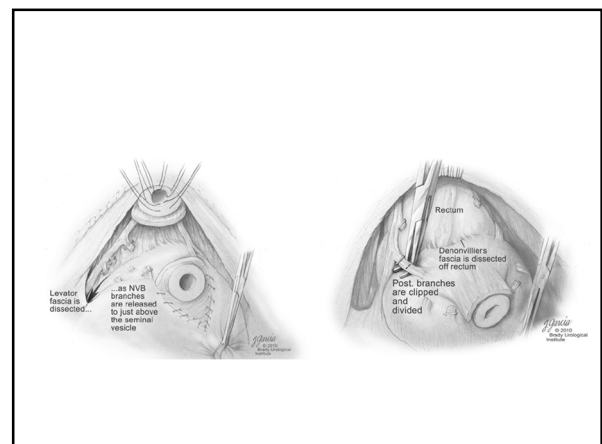
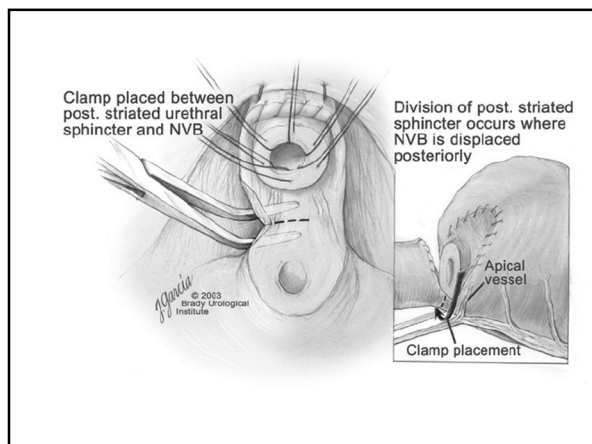
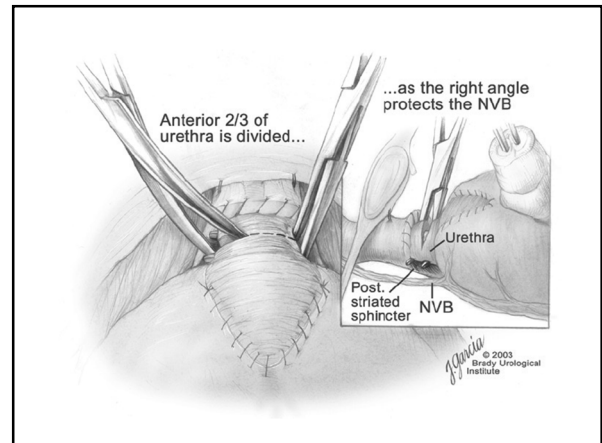
Anatomic Prostatectomy





Anatomic Prostatectomy: Steps

- Incise Endopelvic Fascia
- Divide the pubo-prostatic ligaments
- Preserve any accessory Pudendal arteries (~5% pts.)
- Suture ligate the dorsal venous complex
- Meticulous apical dissection after dividing DVC
- Retrograde dissection of the prostate



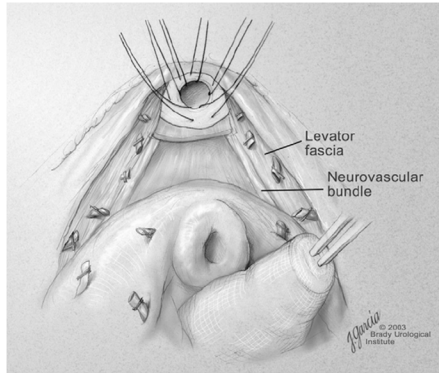
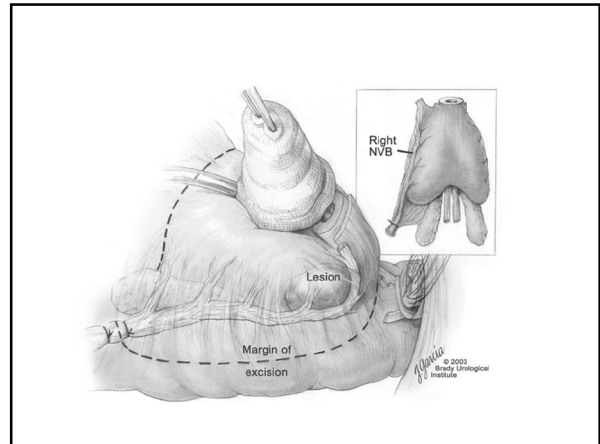


Figure 102-21. A view of the completed dissection. (© Brady Urological Institute.)



When to excise the NVB

- Pre-OP
 - Extensive perineural invasion on biopsy
 - Large volume high grade disease
 - DRE or MRI suspicion of involvement
- Intra-Op
 - Induration of levator fascia
 - Tactile sense that NVB adherent to capsule

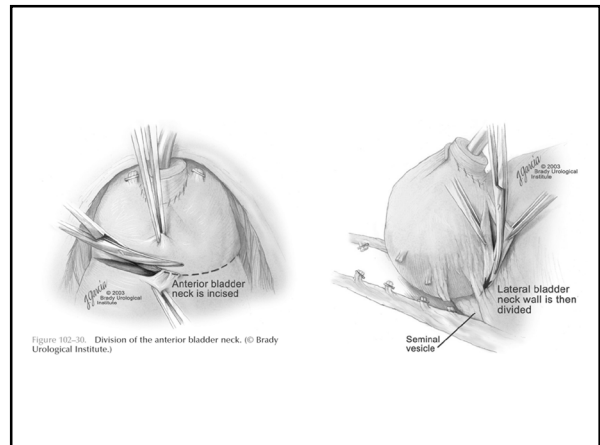


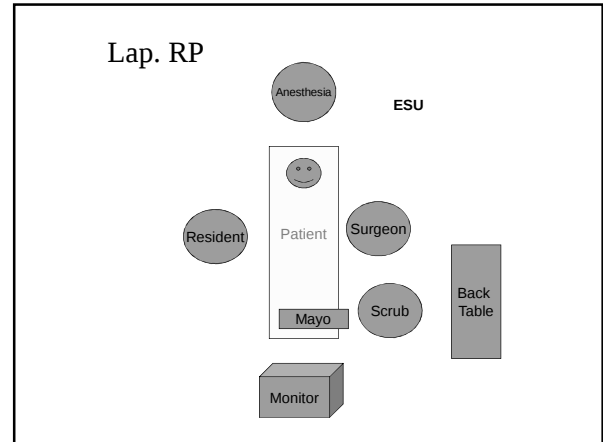
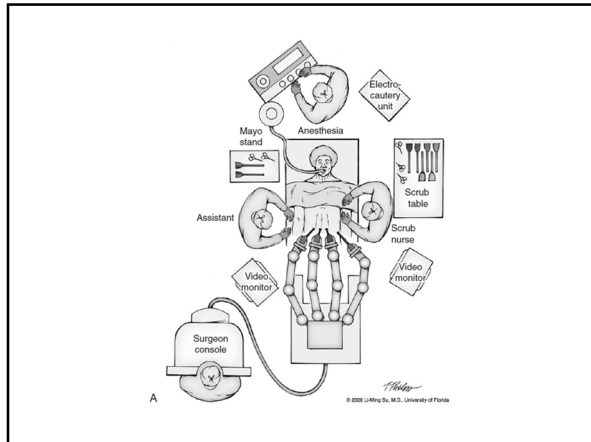
Figure 102-23. Division of the anterior bladder neck. (© Brady Urological Institute.)

Open Retropubic Prostatectomy

- Minimal mortality (0.2%)
- Thromboembolic events ~2%
- Bladder neck contracture 0.5-10%

Open Retropubic Prostatectomy

- Bladder neck preservation
 - No to small benefit to time to continence
 - May have higher BN contracture rate and pos. margin rate
- Seminal Vesicle sparing
 - Concept is that SVI rarely extends more than 1 cm from prostate
 - Potentially less damage to pelvic nerves if SV tips left in situ
 - Data are ambiguous



Trans- v. Extraperitoneal Lap. RP

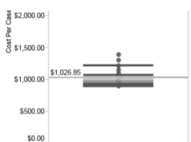
- Shorter OR time and hospital stay
- Easier positioning; minimal Trendelenburg
- Less frequent need for adhesiolysis
- ?Less short-term bladder instability
- ?Less long-term risk if post-op XRT
 - Open peritoneum may allow bowel to drop into pelvis, potentially compromising later pelvic XRT if warranted

Robot v. Pure Lap

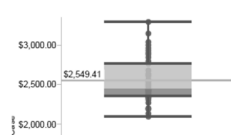
- Robot most often transperitoneal
- Robot more expensive
- Robotic surgeons lack tactile feedback
- Robotic surgeons rely on a potentially “rogue” bedside assistant
- Only the console surgeon has 3-D visualization v. entire OR team w pure lap

Prostatectomy Cost per case

Lap RP Cost



Robotic RP Cost



Prostatectomy Costs per year

OR Supply expense for prostatectomy by procedure (all BJH Surgeons)

Procedures	Cases	Cost Per Case (3)	Total OR supply expense
Prostatectomy Radical Lapa..	203	\$983	\$199,739
Prostatectomy Robotic Assis..	219	\$2,480	\$542,597

Radical Prostatectomy Trends in the United States: 1998 to 2011

Mark D. Tyson II, MD; Paul E. Andrews, MD; Robert F. Fernigni, MD; Mitchell R. Humphreys, MD; Alexander S. Parker, PhD; and Erik P. Castle, MD



FIGURE 1. Quarterly procedure rates of RP by surgical approach. The area plot indicates the quarterly procedure rate (y-axis) of open radical prostatectomy (RP) (orange), laparoscopic RP (which includes robotic RP) before the fourth quarter of 2008 (blue), and robotic RP (brown) from 1998 to 2011. The x-axis represents the time in calendar-year quarters. RP = radical prostatectomy.

Mayo Clin Proc. 2016;91(1):10-16

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Table 5. Perioperative Complication Rates of Open versus Robotic RP

Study	Complication Rates- Open RP	Complication Rates- Robotic RP	p-Value
Lowrance ⁶⁰	24% (n=4,697)	21% (n=1,006)	0.04
Hu ⁶¹	23% (n=6,899)	22% (n=1,938)	0.31
Williams ⁶²	17.1% (n=14,665)	12.5% (n=4,052)	<0.001
Trinh ⁶³	11.1% (n=7,389)	8.2% (n=11,889)	<0.001
Kowalczyk ⁶⁴	29.8% (n=58,638)	19.6% (n=19,594)	<0.001
Carlsson ⁶⁵	45% (n=485)	9.7% (n=1,253)	—
Krambeck ⁶⁶	5% (n=586)	8% (n=294)	0.064
Tewari ⁶⁷	20% (n=100)	5% (n=200)	<0.05
Ficarra ⁶⁸	10.4% (n=105)	9.7% (n=103)	0.85
Di Pietro ⁶⁹	37% (n=75)	40% (n=75)	0.65

*Unadjusted overall complication rates. Studies from Lowrance et al, Hu et al, Williams et al, Trinh et al, and Kowalczyk et al. are population-based studies.

Table 6. Oncologic Outcomes of Open versus Robotic RP: Surgical Margins

Study	Surgical Margins- Open RP	Surgical Margins- Robotic RP	p-Value
Memor ⁷¹	29% (n=30)	26% (n=30)	0.77
Ahlering ⁷²	29% (n=60)	16.7% (n=60)	0.64
Tewari ⁷³	23% (n=100)	9% (n=200)	<0.05
Krambeck ⁶⁶	17% (n=586)	16% (n=294)	0.6
Ou ⁷⁴	20% (n=30)	50% (n=30)	0.015
Ficarra ⁷¹	21% (n=105)	34% (n=103)	0.023
Kim ⁷⁵	24.7% (n=235)	27.1% (n=528)	0.49
Schroek ⁷⁶	28% (n=435)	29% (n=362)	0.7
Barocas ⁷⁷	30% (n=491)	20% (n=1,413)	<0.01
Breyer ⁷⁸	16% (n=695)	18% (n=293)	0.25
Magheli ⁷⁹	14.4% (n=522)	15.5% (n=522)	0.026
Thompson ⁸⁰	18.8% (n=674)	19.2% (n=837)	0.85

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Table 8. Functional Outcomes of Open versus Robotic RP: Urinary Continence and Potency

Study	Urinary Continence (% at 12 months)- Open RP	Urinary Continence (% at 12 months)- Robotic RP	Potency (% at 12 months)- Open RP	Potency (% at 12 months)- Robotic RP
Krambeck ⁶⁶	94% (n=564)	92% (n=286)	63% (n=417)	70% (n=203)
Kim ⁷⁵	—	—	28% (n=122)	57% (n=373)
Ficarra ⁷¹	88% (n=105)	97% (n=103)	49% (n=41)	81% (n=64)
Di Pietro ⁷²	80% (n=75)	89% (n=75)	26% (n=47)	55% (n=22)
Thompson ⁸⁰	65.1% (n=230)	57.1 (n=379)	26.2% (n=230)	28.8% (n=379)

ALIA On-line Curriculum

Robot-assisted radical prostatectomy vs laparoscopic and open retropubic radical prostatectomy: functional outcomes 18 months after diagnosis from a national cohort study in England

Results: In all, 2219 men (77.0%) responded; 1310 (59.0%) had RARP, 487 (21.9%) LRP and 422 (19.0%) ORP. RARP was associated with slightly higher adjusted mean EPIC-26 sexual function scores compared with LRP (3.5 point difference; 95% CI: 1.1–5.9, P=0.004) or ORP (4.0 point difference; 95% CI: 1.5–6.5, P=0.002), which did not meet the threshold for a minimal clinically important difference (10–12 points). There were no significant differences in other EPIC-26 domain scores or HRQoL.

Conclusions: It is unlikely that the rapid adoption of RARP in the English NHS has produced substantial improvements in functional outcomes for patients.

BRITISH JOURNAL OF CANCER

Functional outcomes after RARP, LRP or ORP

Table 3. Relationship between patient-reported outcomes post-procedure and type of radical prostatectomy ORP, LRP and RARP; overall domain scores for EPIC-26 and EQ-5D-5L, and adjusted differences for RARP vs LRP and RARP vs ORP

	RARP	LRP	ORP	RARP vs LRP Adjusted difference (95% CI)	RARP vs ORP Adjusted difference (95% CI)
No. of patients	1310 (59.0%)	487 (21.9%)	422 (19.0%)		
EPIC-26					
Urinary (incont)					
Mean (SD)	70.5 (28.0)	68.5 (29.5)	70.1 (27.3)	1.2 (–1.7, 4.2) P=0.4	–0.3 (–3.1, 2.1) P=0.9
Missing	70	28	31		
Urinary (int./stab.)					
Mean (SD)	91.4 (11.8)	91.2 (11.7)	91.0 (11.7)	–0.18 (–1.8, 1.5) P=0.8	1.02 (–0.70, 2.7) P=0.2
Missing	183	70	78		
Sexual					
Mean (SD)	24.4 (24.7)	20.1 (22.3)	18.6 (20.5)	3.5 (1.1, 5.9) P=0.004	4.0 (1.5, 6.5) P=0.002
Missing	33	7	14		
Bowel					
Mean (SD)	94.2 (11.9)	93.8 (11.7)	94.2 (12.7)	0.30 (–1.1, 1.7) P=0.7	0.37 (–1.9, 1.1) P=0.6
Missing	90	38	42		
Harmonial					
Mean (SD)	86.8 (16.3)	8.6 (16.3)	86.4 (18.2)	–0.32 (–2.1, 1.5) P=0.7	0.75 (–1.2, 2.7) P=0.4
Missing	72	29	42		
EQ-5D					
Mean (SD)	0.90 (0.14)	0.89 (0.15)	0.89 (0.14)	0.00 (–0.01, 0.02) P=0.66	–0.01 (–0.01, 0.02) P=0.2
Missing	16	7	12		

Abbreviations: LRP = laparoscopic radical prostatectomy; ORP = open retropubic radical prostatectomy; RARP = robot-assisted radical prostatectomy.

The Australian laparoscopic non robotic radical prostatectomy experience – analysis of 2943 cases (USANZ supplement)

Table 4 Oncological and Functional Outcomes of Australian LRP Series Compared to High-Volume Published Data of Open, Laparoscopic and Robotic Prostatectomy.

Variable	Our series	ORP*	LRP*	RALP*
pT2 (%)	73.6	64.3	64	78.7
pT3 (%)	26.2	31.5	32.6	20.5
pT2 PSM (%)	9.8	16.8	12.4	9.6
pT3 PSM (%)	32.6	42	39.2	37.1
Overall PSM (%)	15.9	24	21.3	13.6
Mean 12 month continence	91 [†]	80	85	92
Mean 12 month potency	47 [‡]	29	55	71

*Coeiro et al. (2010). †Data on 5 surgeons. ‡Data on 4 surgeons.

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Published by John Wiley & Sons Ltd. www.bju.org

LRP: Personal Series

- 2235 through 2017
- Age: 62.1 +/-6.9
- BMI: 29.1 +/-14.6
- PSA: 7.8 +/- 8.8
- 11% susp. DRE
- 93.6 % white
- 38% + Fam Hx

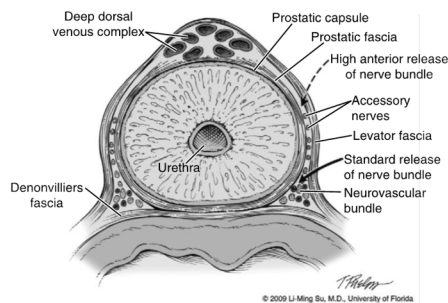
LRP: Personal Series

- Op Time: 127 +/- 33 min.
- RP Gleason: 19% 6/ 65% 7/ 11% 8-10
- PSM: 7.4% T2/ 23% overall
- 15.4% PSA recurrence
- Continence after 6 mon: 92%
- Erection after 1 year: 54.2% without meds
- 25.1% with meds

Extraperitoneal Lap RP

- Combines advantages of open and robotic approaches in a cost-effective way
- Learning curve similar for all 3 approaches.

Retzius-Sparing Robotic Px



Salvage Radical Prostatectomy

- Reserved for men in excellent health whose initial tumor was apt to be cured by surgery and whose re-staging after recurrence is also favorable.
- MRI and PET imaging (Choline or fluciclovine) recommended
- Intraoperative complications acceptable (~2% rectal injury)
- Continence in ~85% and potency up to 15%

Salvage Radical Prostatectomy

- Oncologic outcomes:
 - Local control excellent
 - PSA recurrence in ~40% at 5 years
 - Uncertain impact on overall survival
- Most series use the open technique, but more recently laparoscopic and robotic-assisted techniques are reported w similar outcomes

Management of Post-Prostatectomy Biochemical Recurrence

- Current definition requires a PSA > 0.2
- Occurs in 20-30%
- Half of men destined to recur will do so within 3 years; 80% within 5 years and ~99% within 10 years
- Important considerations for treatment:
 - Interval between surgery and recurrence
 - Pathologic findings on RP
 - PSA kinetics

Defining BCR After RP

AUA ^[a]	PSA >0.2 ng/mL measured ≥6 weeks post-RP and confirmatory testing showing persistent PSA >0.2 ng/mL
EAU-ESTRO-SIOG ^[b]	PSA ≥0.2 ng/mL post-RP and in 2 sequential measurements
PSA Working Group ^[c]	PSA ≥0.4 ng/mL followed by a confirmed subsequent rise

a. Cookson MS, et al. *J Urol*. 2007;177:540-545; b. Mottet N, et al. *Eur Urol*. 2017;71:618-629; c. Scher HI, et al. *J Clin Oncol*. 2004;22:537-556.

Clinical Dilemmas in men with BCR

- Cannot tell where recurrent disease is located
- Absolute PSA levels tend to correlate with disease burden and risk for metastasis
- Shorter PSADT associated with higher risk of metastases
- Time to BCR is prognostic in most, but not all, studies

a. Danesh OM, et al. *Front Oncol*. 2012;2:1-6; b. Paller CL, et al. *Clin Adv Hematol Oncol*. 2013;11:14-23.

Diagnostic Evaluation of Patients With BCR

- No guidelines on frequency of evaluation in men with BCR
- NCCN Guidelines® note:
 - Factors affecting BCR imaging use after RP
 - Risk group before surgery
 - Gleason score
 - Stage
 - Serum PSA
 - PSADT after recurrence
 - Cross-sectional imaging and conventional Tc-99m bone scans are rarely positive in asymptomatic men with PSA < 10 ng/mL
 - Imaging should be performed more frequently when PSADT ≤ 8 mo

NCCN® website

NCCN
National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 3.2018
Prostate Cancer

NCCN.GU
1.0

Table 2. Summary of Main PET/CT Imaging Tracers Studied in Prostate Cancer*

Tracer	Half-life (min)	Cyclotron	Mechanism of action	Excretion	Sensitivity (%) ^a	Specificity (%) ^a	FDA Status	Panel Recommendation
C-11 choline	20	Onsite	Cell membrane synthesis	Hepatic	32–93	40–93	• Cleared	May be used for detection of biochemically recurrent small-volume disease in soft tissues
F-18 fluciclovine	110	Regional	Amino acid transport	Renal	37–90	40–100	• Cleared	May be used for detection of biochemically recurrent small-volume disease in soft tissues
F-18 NaF	110	Regional	Adsorption within bone matrix	Hepatic	87–100	62–89	• Cleared	May be used after bone scan for further evaluation of equivocal findings
C-11 acetate	20	Onsite	Lipid synthesis	Lung	59–69	83–98	• Not cleared	May be used in clinical trial or registry
Ga-68 PSMA	68	Generator (no cyclotron)	PSMA analog	Renal	76–86	86–100	• Not cleared	May be used in clinical trial or registry

* Interpret with caution; new studies used biopsy/surgery as gold standard; see *Nuclear Imaging*, above, for references.

* Interpret with caution; few studies used biopsy/surgery as gold standard; see Nuclear Imaging, above, for references.

¹¹C-Choline-PET/CT Sensitivity by PSA Level

- Analysis of 358 patients post-RP with BCR (≥ 2 consecutive PSA measurements > 0.2 ng/mL)
 - Overall sensitivity /specificity: 85% /93%
- Detection rate by PSA level:
 - PSA 0.2 to 1 ng/mL: 19%
 - PSA 1 to 3 ng/mL: 46%
 - PSA > 3 ng/mL: 82%
- Package insert for ¹¹C-choline notes reduced sensitivity and specificity in patients with PSA levels < 2.0 ng/mL.

a. Giovacchini G, et al. *Eur J Nucl Med Mol Imaging*. 2010;37:301-309.
b. Choline C11 PI 2015.

11C-Choline PET/CT in Patients With BCR Systematic Review

Parameter, %	All 18 Studies (N = 2126)	10 Studies Reporting Local Recurrence (n = 993)	7 Studies Reporting Nodal Metastases (n = 752)	8 Studies Reporting Bone Metastases (n = 775)
Pooled detection rate (95% CI)	62 (53, 71)	27 (16, 38)	36 (22, 50)	25 (16, 34)
No. of studies assessable for sensitivity/specificity (pts, n)	12 (1270)	6 (491)		
Pooled sensitivity (95% CI)	89 (83, 93)	61 (40, 80)		
Pooled specificity (95% CI)	89 (73, 96)	97 (87, 99)		

Fanti S, et al. *Eur J Nucl Med Mol Imaging*. 2016;43:55-69.

18F-Fluciclovine PET/CT in BCR PC: BED-001 Study

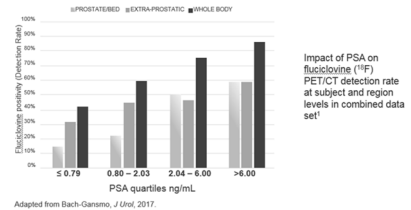
- Retrospective analysis of 18F-fluciclovine in 596 patients who received ≥ 1 injection for the detection of suspected BCR after RP or RT
- Overall detection rate was 67.7%

Detection Rate by Site

Site	Detection Rate, %
Prostate bed	38.7
Pelvic lymph nodes	32.6
Extrapelvic metastases	26.2

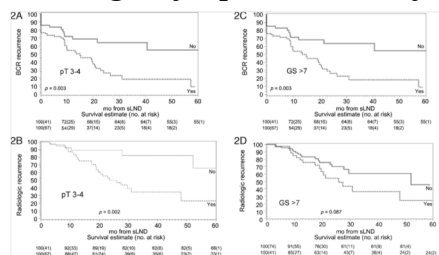
- Overall detection rate for patients with PSA < 0.8 ng/mL was 41.4%

Bach-Gansmo T, et al. *J Urol*. 2017;197:676-683.



1. Bach-Gansmo T, Nanni C, Nish PT, et al. *J Urol*. 2017;197:676-683.

Salvage Lymphadenectomy



EUROPEAN UROLOGY FOCUS 2 (2016) 522-531

Surgery for Prostate Cancer

- It works for the right patient and the right tumor
- Approach-open, Lap or Robotic Asst Lap—doesn't seem to matter significantly in terms of outcomes; but cost of robotic approach significantly higher than others
- Salvage surgery after XRT or isolated nodal metastases reasonable in men whose initial tumor was curable.

Radiation For Prostate Cancer in the Definitive and Post-Operative Setting

Paul L. Nguyen, MD
Vice Chair for Clinical Research
Genitourinary Disease Center Leader for Radiation Oncology
Dana-Farber/Brigham and Women's Cancer Center
Associate Professor
Harvard Medical School

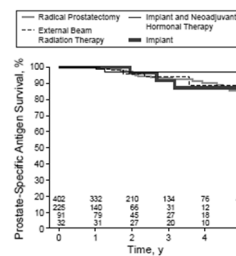
Disclosures

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 - Augmenix
 - Bayer
 - Blue Earth
 - Janssen
- Research Funding:
 - Janseen, Astellas
- Equity
 - Augmenix

NCCN Low-Risk Prostate Cancer – Many options

- Active Surveillance
- Radical Prostatectomy
- External Beam Radiation Alone (No Hormones)
 - Standard Course: 79.2Gy/1.8Gy per fraction (44 fxs), 78Gy/2Gy/fx (39 fxs)
 - Hypofractionated: 70Gy/2.5Gy per fx (28fxs), 60Gy/3.0Gy per fx (20fxs)
 - SBRT: Stereotactic Body RT: 36-40Gy in five fractions of 7.25-8Gy
- Brachytherapy
 - Low Dose Rate (Single permanent seed implant): I-125, Pd-103, Cs-131
 - High Dose Rate (Temporary Catheters, 4 fxs): Ir-192

D'Amico, JAMA 1998 – Low-Risk



- Low-Risk
 - cT1c-T2a
 - Gleason 6 or less
 - PSA<10
- RP, EBRT, Brachy had similar outcome

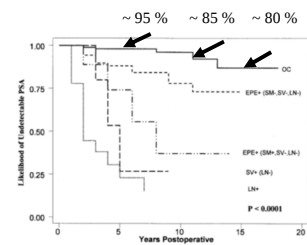
Figure 1.—Estimated prostate-specific antigen outcome for low-risk patients stratified by treatment modality. All pairwise *P* values are more than .25.

Brachy Outcomes (Low-Risk)

Study	n	PSA control	F/U (yrs)	
Merrick	160	97 %	5	~ 95 %
Zelevsky	319	96 %	5	
Blasko	230	84 %	9	~ 85 %
Grimm	125	87 %	10	
Stone	279	78 %	10	~ 80 %
Potters	481	88 %	12	
Sylvester	215	86 %	15	

Merrick IJROBP 2001, Zelevsky IJROBP 2007, Blasko IJROBP 2000, Grimm IJROBP 2001, Stone J Urol 2005, Potters J Urol 2005, Sylvester IJROBP 2011

Johns Hopkins - Walsh @ 15 yrs



Khan Urology 2003, Han Urol Clin North Am 2001

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COMMENTS AND CONTROVERSIES

Brachytherapy: Where Has It Gone?

Daniel G. Petereit, *Rapid City Regional Cancer Center, Rapid City, SD*
Steven J. Frank, *University of Texas MD Anderson Cancer Center, Houston, TX*
Akila N. Viswanathan, *Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
Beth Erickson, *Medical College of Wisconsin, Milwaukee, WI*
Patricia Eifel, *University of Texas MD Anderson Cancer Center, Houston, TX*
Paul L. Nguyen, *Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
David E. Wazer, *Tufts Medical Center, Tufts University School of Medicine, Boston, MA, and Rhode Island Hospital, The Alpert Medical School of Brown University, Providence, RI*

Decrease in Brachytherapy Monotherapy for Prostate CA

- Muralidhar, et al Brachytherapy 2015
- US SEER Population

A Brachytherapy monotherapy use over time

Decline was contemporaneous with rise in IMRT (2005-2012) which reimburses significantly higher

Driven by Decrease in Low-Risk Treatments Intermediate is a greater proportion

B Percentage of prostate cancer patients treated with brachytherapy monotherapy

— % Low-risk patients opting for BT — % Int-risk patients opting for BT
..... % High-risk patients opting for BT

Only 1% of Academic Practices Do >1 Case per week

Orio PF, JROBP 2016

Academic Practices (%)	2004	2005	2006	2007	2008	2009	2010	2011	2012
≤12	56.36	53.16	49.06	54.04	60.12	65.77	62.89	66.44	73.72
13-52	36.97	35.87	43.40	37.89	34.36	29.53	32.47	28.19	24.82
>53 cases/week	6.67	6.96	7.55	8.07	5.52	4.70	4.95	5.37	1.46

PROTECT RCT Similar Survival and PFS for Surgery and Radiation in Low/Favorable Intermed Risk PCa

A Prostate Cancer-Specific Survival

No. at Risk 1643 1628 1605 1575 1286 746

B Freedom from Disease Progression

No. at Risk 1643 1601 1533 1467 1175 666

NEJM 2016

Mild Hypofractionation is Non-Inferior for PFS Through 6 yrs for Low/Int Risk. May Have Slightly More GI/GU Toxicity

Trial	Risk Group	Std	HYP0	FU Yrs	DFS HR	Gr2/3 GI Toxicity Hypo vs. Std	Gr 2/3 GU Toxicity Hypo vs Std
RT0G 04-15	LOW	73.8Gy/41fx	70Gy/28fx	5.0	0.85 (0.64-1.14)	HR 1.55-1.59 for Late tox	HR 1.31-1.56 for Late tox
PROFIT	INT	78Gy/39fx	60Gy/20fx	6.0	0.97 (0.77-1.2)	No Diff	No Diff
CHHIP	LOW/INT (12% HIGH, 6% GI 8-10)	74Gy/37fx	60Gy/20fx	5.2	0.84 (0.68-1.03)	38% vs 25% Gr 2+ Acute Tox	No Diff

JCO 2016, JCO 2017, Lancet Oncol 2016

ASTRO Model Policies

STEREOTACTIC BODY RADIATION THERAPY (SBRT)

Prostate Cancer:

Many clinical studies supporting the efficacy and safety of SBRT in the treatment of prostate cancer have been published. At least one study has shown excellent five year biochemical control rates with very low rates of serious toxicity. Additionally, numerous studies have demonstrated the safety of SBRT for prostate cancer after a follow-up interval long enough (two to three years) to provide an opportunity to observe the incidence of late GU or GI toxicity. While it is necessary to observe patients treated for prostate cancer for extended intervals to gauge the rate of long term (beyond 10 years) biochemical control and overall survival, the interim results reported appear at least as good as other forms of radiotherapy administered to patients with equivalent risk levels followed for the same duration post-treatment.

It is ASTRO's opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease.

Updated 4-17-13

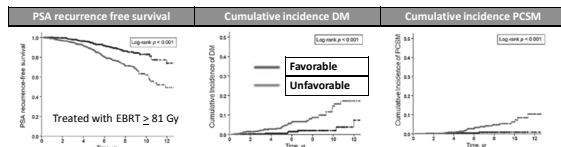
Courtesy of Karen Hoffman, MD Anderson

Randomized trials of SBRT vs. Conventional RT

- HYPO-RT-PC, Sweden, n=1200, Widmark
 - Hypofractionated radiotherapy of intermediate/high risk and no ADT
 - 78 Gy in 2 Gy fractions vs. 42.7 Gy in 6.1 Gy fractions QOD over 2.5 weeks
 - Reported at ESTRO 2018 – 5yr FU,
 - Similar BRFS: 83.8% std vs. 83.7% SBRT bRFS HR=0.992 (0.735-1.307)
 - Similar Late Gr 2+ Urinary Tox: 3.5% std vs. 2.5% SBRT
 - Similar Late Gr 2+ Rectal Tox: 2.3% std vs. 1.3% SBRT
- PACE Trial, UK, n=1700, Low/Int risk (RP vs. SBRT or Conv RT vs. SBRT)
 - 78 Gy in 2 Gy fractions vs. 36.25 in 7.25 Gy fractions
 - Nicholas Van As

Intermediate-risk prostate cancer is a heterogeneous disease

- Unfavorable intermediate-risk: Gleason pattern 4+3=7, $\geq 50\%$ biopsy cores, or multiple intermediate risk factors
- Favorable intermediate-risk: all others



Courtesy of Karen Hoffman, MD Anderson

Zumsteg European Urology 2013 62:895

Trend towards avoiding ADT in Favorable Intermediate Risk

Favorable:

- Gleason 3+4
- PSA <10
- OR
- Gleason 6
- PSA 10-20

Unfavorable:

- Gleason 4+3
- $\geq 50\%$ of cores positive
- Multiple intermediate factors

Favorable Intermediate Risk Can be Treated like Low Risk Prostate CA

Zumsteg, et al Eur Urol 2013

NCCN Favorable Intermediate Risk Prostate Cancer – Treat Like Low Risk

- Active Surveillance (But only for select cases)
- Radical Prostatectomy
- External Beam Radiation Alone (No Hormones)
 - Standard Course: 79.2Gy/1.8Gy per fraction (44 fxs), 78Gy/2Gy/fx (39 fxs)
 - Hypofractionated: 70Gy/2.5Gy per fx (28fxs), 60Gy/3.0Gy per fx (20fxs)
 - SBRT: Stereotactic Body RT: 36-40Gy in five fractions of 7.25-8Gy
- Brachytherapy
 - Low Dose Rate (Single permanent seed implant): I-125, Pd-103, Cs-131
 - High Dose Rate (Temporary Catheters, 4 fxs): Ir-192

French Experience w/Brachytherapy Monotherapy in Favorable Int. Risk

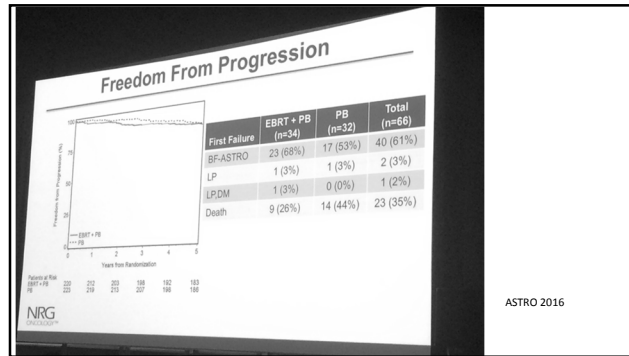
- Cosset, et al, IJROBP 2008

	5-yr bRFS
Low-Risk	97%
PSA 10-15, Gleas ≤ 6	95%
PSA <10, Gleas 7	94%
PSA 10-15, Gleason 7	88%

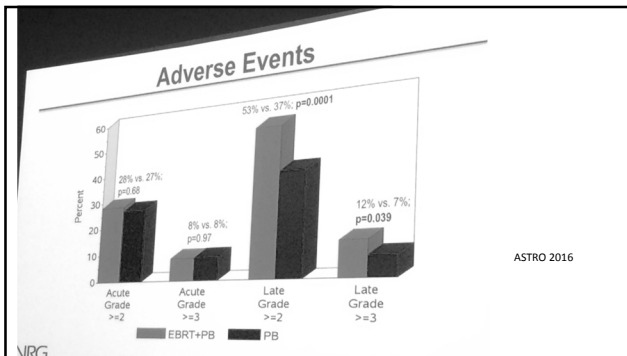
Of note, D90s typically 180 in the series

Supplemental EBRT is Not Needed With Brachy for Favorable Intermediate Risk

- RTOG 02-32 (Prestidge, ASTRO Plenary 2016)
 - N=588, "Favorable intermediate Risk"
 - cT1c-T2b w/GS6 & PSA10-20 or GS7 & PSA<10
 - 67% T1; 89% GS≤7 and PSA<10
 - Brachy alone (I-125 or Pd-103) vs. 45Gy EBRT + Brachy boost
 - Accrued, but closed for fertility after 6.7 yrs and 443pts evaluable
 - PSA FFS was 85% for B+EBRT, and 86% for B
 - Late GU toxicity slightly higher in B+EBRT (7% vs. 3% late Gr. 3+ GU)



ASTRO 2016



ASTRO 2016

HDR Brachy as Monotherapy

- HDR has been fully accepted as a boost but acceptance as monotherapy was slow due to lack of data
- 3 series published in 2016 led to NCCN guideline inclusion

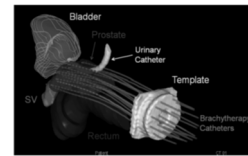
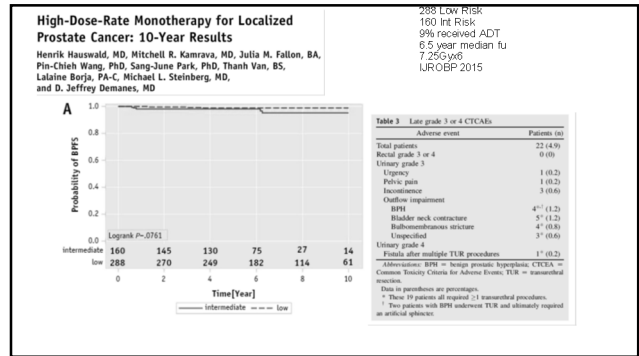
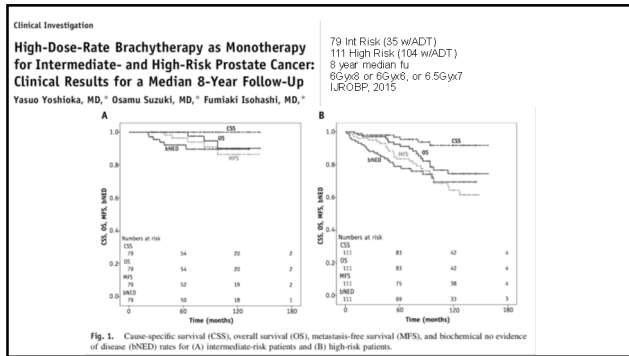


Fig. 1. Three-dimensional virtual image reconstruction of a high-dose-rate implant, with red representing source dwell positions. Abbreviation: SV, seminal vesicle.

Outcomes Associated With 3 Treatment Schedules of High-Dose-Rate Brachytherapy Monotherapy for Favorable-Risk Prostate Cancer John S. Cozzitelli, MD, PhD, Justin S. Elliott, MD, PhD, John S. Cozzitelli, MD, PhD, Hong Ye, MD, Michelle Wallace, MD, PhD, David J. Slamon, MD, PhD, Peter T. Pisters, MD, PhD, and Daniel J. Slamon, MD, PhD			
		68% Low Risk 32% Intermediate Risk 4.1 year median fu 4Gy/2, 12Gy/2, or 13.5Gy/2 UOBBP, 2015	
Table 6 Clinical outcomes for all patients at 5 years			
Outcome	38 Gy/4 (95% CI, no. of patients at risk)	24 Gy/2 (95% CI, no. of patients at risk)	27 Gy/2 (95% CI, no. of patients at risk)
Overall survival	98% (95.1-98.9, 177)	99% (91.0-99.8, 8)	100% (n/a, 1)
Cause-specific survival	100% (n/a, 176)	100% (n/a, 8)	100% (n/a, 1)
Biochemical control	97% (93.5-98.7, 117)	87% (68-95.1, 5)	90% (63.8-97.6, 0)
Local control	91% (87.4-93.8, 160)	85% (70.0-92.6, 7)	81% (74.9-97.2, 0)
Distant metastases-free survival	100% (n/a, 177)	100% (n/a, 8)	100% (n/a, 1)
Disease-free survival	89% (84.8-91.9, 160)	84% (69.2-91.6, 7)	91% (74.9-97.2, 0)
			.32

Table 2 Acute toxicity based on dosing schedule for all patients (N=494)									
Toxicity	38 Gy/4 (n=319)			24 Gy/2 (n=79)			27 Gy/2 (n=96)		
	G1	G2	G3	G1	G2	G3	G1	G2	G3
Frequency/urgency	42%	14%	3%	35%	18%	0%	43%	14%	1%
Dysuria	25%	7%	0%	15%	6%	1.5%	22%	3%	0%
Retention	16%	10%	1%	18%	5%	0%	14%	0%	0%
Incontinence	5%	2%	0.4%	0%	0%	0%	1%	0%	0%
Hematuria	5%	0%	0%	1.5%	1.5%	0%	0%	5%	0%
Diarrhea	10%	2%	0%	8%	0%	0%	6%	0%	0%
Rectal pain/tenesmus	5%	1%	0%	5%	0%	0%	0%	1%	0%
Rectal bleeding	3%	0%	0%	3%	0%	0%	0%	0%	0%
Proctitis	1%	0.5%	0%	0%	0%	0%	0%	1%	0%

Table 3 Chronic toxicity based on dosing schedule for all patients (N=494)									
Toxicity	38 Gy/4 (n=319)			24 Gy/2 (n=79)			27 Gy/2 (n=96)		
	G1	G2	G3	G1	G2	G3	G1	G2	G3
Frequency/urgency	35%	19%	1%	37%	21%	0%	44%	20%	3%
Dysuria	18%	8%	1%	20%	3%	0%	24%	5%	4%
Retention	19%	5%	2%	17%	0%	0%	41%	4%	0%
Incontinence	7%	2%	0.8%	13%	3%	0%	6%	1%	1%
Hematuria	6%	7%	0.8%	4%	0%	0%	11%	0%	0%
Diarrhea	6%	1%	0%	12%	1%	0%	13%	0%	0%
Rectal pain/tenesmus	4%	0.4%	0%	6%	0%	0%	6%	1%	0%
Rectal bleeding	8%	2%	0%	7%	1%	0%	3%	0%	0%
Proctitis	1%	1%	0%	3%	3%	0%	5%	1%	0%



NCCN Unfavorable Intermediate Risk

Generally adds short-course ADT to radiation

- RP
- EBRT + 4 to 6 months ADT
- EBRT + Brachy Boost (+/- 4 to 6 months ADT)

ADT Potentiates Radiation Damage by Blocking DNA Damage Repair

RESEARCH ARTICLE

A Hormone-DNA Repair Circuit Governs the Response to Genotoxic Insult

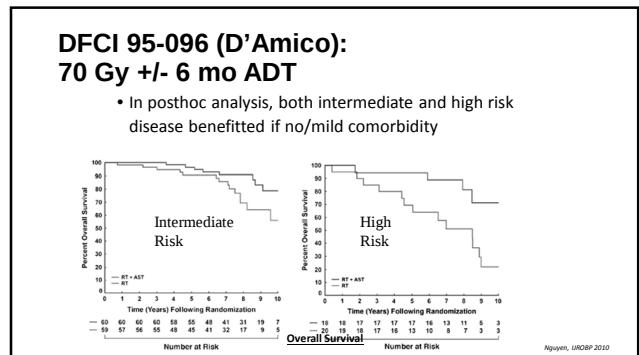
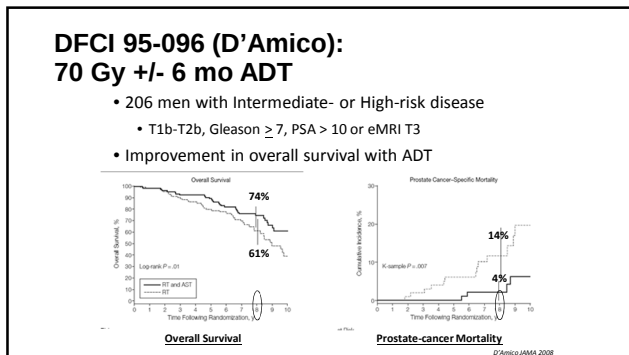
Jonathan F. Goodwin¹, Matthew J. Schiewer¹, Jeffrey L. Dean¹, Randy S. Schenck^{1,2}, Renshi de Lencastre¹, Sumin Han¹, Teng Ma¹, Robert B. Den^{1,3}, Adam P. Dickert^{1,4}, Felix Y. Feng^{1,6,7}, and Karen E. Knudsen^{1,2,3,4}

RESEARCH BRIEF

Androgen Receptor Signaling Regulates DNA Repair in Prostate Cancers

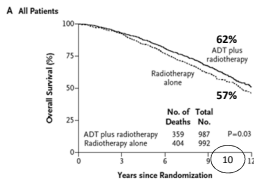
William R. Polkinghorne^{1,4}, Joel S. Parker^{1,11}, Mao X. Lee¹, Elizabeth M. Kahn¹, Daniel E. Spratt¹, Philip J. Iaquineta¹, Vivian K. Arora^{1,12}, Wei-Feng Yoo¹, Ling Cai¹, Depu Zhang¹, Brett S. Cawley^{1,3}, Yu Chen^{1,3}, Philip A. Watson¹, Neal P. Shah¹, Sho Fujisawa¹, Alexander G. Goggin¹, Anuradha Gopalani¹, Haley Hottelmyer¹, John Wongpradit¹, Peter T. Scardone¹, Michael J. Zelefsky¹, Maria Jasin¹, Jayanta Chaudhuri¹, Simon N. Powell¹, and Charles L. Sawyers¹

Cancer Discover 2013



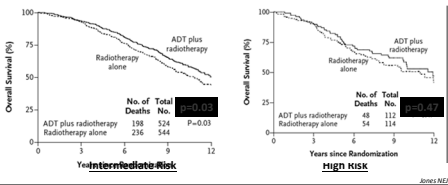
**RTOG 94-08:
66 Gy +/- 4 mo ADT**

- 1,979 men w/ T1b-T2b, and PSA < 20
- 35% low, 54% intermediate; 11% high risk
- Improvement in overall survival with ADT



**RTOG 94-08:
66 Gy +/- 4 mo ADT**

- Only intermediate-risk benefited 4 mo ADT
- Low-risk does not need hormones
- For high-risk, may not be enough



**The Trials Used Lower Doses Than
Current Standard (>75Gy)**

Trial	Dose (Gy)
DFCI	70 Gy
RTOG	66 Gy
TROG	66 Gy

- Is short-course ADT needed for men with intermediate risk prostate cancer treated with dose-escalated (> 75 Gy) radiation?

**Need for ADT with Dose-Escalated EBRT
is Being Studied in RTOG 0815**

S R A R I F	Number of Risk Factors*		R A N D O M I Z E	Arm 1	
	1. One risk factor			Dose-escalated RT alone	
	2. Two or 3 risk factors				
	Comorbidity Status			Arm 2	
	1. ACE-27** grade ≥ 2				Dose-escalated RT combined with short-
	2. ACE-27 grade < 2				term (6 months) androgen blockade (LHRH agonist + antiandrogen)
	RT Modality				
	1. Dose-escalated EBRT				
	2. EBRT + LDR brachytherapy boost				
	3. EBRT + HDR brachytherapy boost				
*Intermediate risk factors: Gleason Score 7***; PSA >10 but ≤20; T-Stage T2b-T2c. Patients with all three intermediate risk factors and ≥ 50% of their sampled biopsy cores involved will <u>not</u> be eligible for this study. Note: The percentage of biopsy cores involved will only be considered with respect to eligibility for those patients with all 3 of the above risk factors (i.e., patients with one or two of the above risk factors are eligible irrespective of the percentage of biopsy cores involved).					
**The "untreated malignancy" section of the ACE-27 form is to be disregarded with respect to the patient's newly diagnosed, untreated prostate cancer.					
***Patients with Gleason score ≥ 8, PSA > 20, or clinical stage > T2c are ineligible for this study.					

**EORTC Trial Suggests ADT Still
Benefits w/Dose Escalated RT**

JOURNAL OF CLINICAL ONCOLOGY

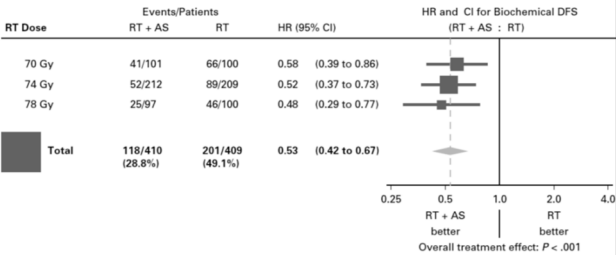
ORIGINAL REPORT

Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991

Michel Bolla, Philippe Maingon, Christian Carrie, Salvador Villa, Peter Kinnis, Philip M.P. Poortmans, Sandhu Sander, Håkan M. van der Stoep-Baas, John Armstrong, Jean-François Beus, Fernando G. Herrera, Bradley Peters, Amerio Slot, Amir Bahl, Rahim Ben-Yosef, Dirk Boehmer, Christopher Scarra, Laurence Remond, Ewald Shaik, Corné Gies, Alphonsus C.M. van den Bergh, and Laurence Collette

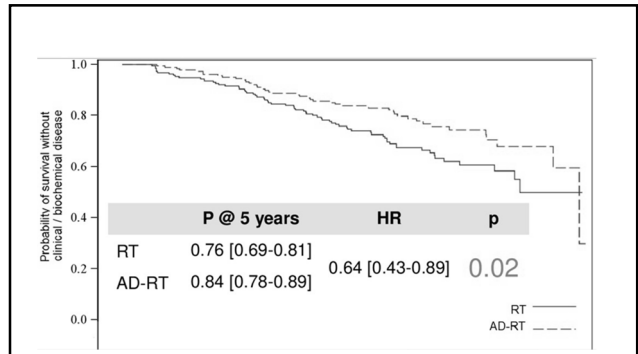
See accompanying editorial doi:10.1200/JCO.2015.66.7320.

EORTC 22911



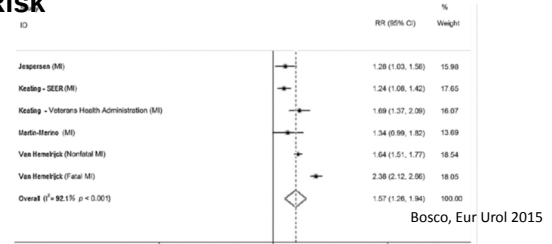
GETUG-14 Confirms that ADT needed w/80Gy

- 377 men w/intermediate risk prostate CA
- 80Gy RT vs. 80Gy RT+ 4 months of ADT
- RT=Prostate+SV to 46Gy, Prostate to 80Gy



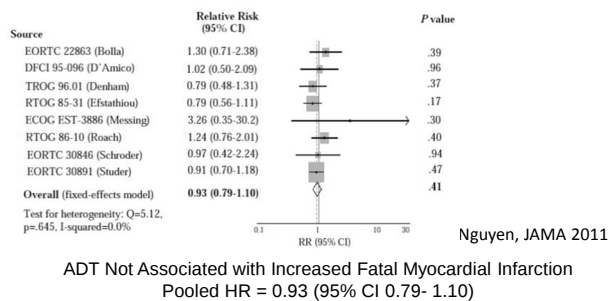
What about cardiac harms of ADT?

Meta-Analysis of Observational Data Finds CV Risk



ADT Associated with Increased Fatal or Non-Fatal Myocardial Infarction
Pooled HR = 1.57 (95% CI 1.26- 1.94)

Meta-Analysis of Randomized Data Finds

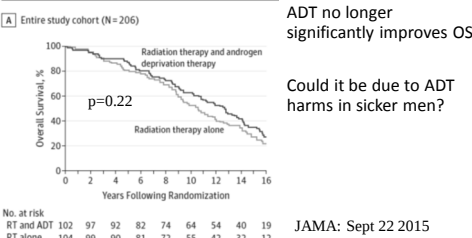


What Could Explain Discrepancy Between Randomized and Observational Data?

- 1) The results from observational data reflect confounding (e.g. sicker pts get ADT)
- 2) The observational results included non-fatal MIs while randomized only looked CV Death
- 3) Perhaps ADT causes harm mainly in men with pre-existing comorbidities, who are under-represented in randomized trials

Is there a subgroup of men who could be harmed by ADT?

D'Amico/DFCI 6 vs 0 Mos Update
16 yrs follow-up, Int/High risk localized



Increased CV Death for Sicker Men on ADT?

	No. of Men	No. of Deaths	No. of Deaths	Cardiac	
				HR (95% CI)	P Value
Age at randomization, per year	206 ^a	156	39	1.02 (0.96-1.08)	.62
Interaction Terms					
None or minimal comorbidity ^b					
RT and ADT	78	53	7	1 [Reference]	.28
RT alone	79	57	11	1.72 (0.64-4.58)	
Moderate or severe comorbidity ^b					
RT and ADT	24	23	15	1 [Reference]	<.001
RT alone	25	23	6	0.17 (0.06-0.46)	
ADT × comorbidity	206	156	39	0.10 (0.03-0.40) ^c	.001

D'Amico
JAMA 2015

Stratification by ACE-27 Comorbidity Scale is Being Studied in RTOG 0815

S T R A T I F I C A T I O N	Number of Risk Factors ^a	Comorbidity Status	RT Modality	Arm
1	1. One risk factor	1. ACE-27 ^b grade ≥ 2	1. Dose-escalated EBRT	Arm 1
2	2. Two or 3 risk factors	2. ACE-27 grade < 2	2. EBRT + LDR brachytherapy boost	Arm 2
3			3. EBRT + HDR brachytherapy boost	

^aIntermediate risk factors: Gleason Score 7^{***}; PSA >10 but ≤20; T-Stage T2b-T2c. Patients with all three intermediate risk factors and ≥ 50% of their sampled biopsy cores involved will not be eligible for this study. Note: The percentage of biopsy cores involved will only be considered with respect to eligibility for those patients with all 3 of the above risk factors (i.e., patients with one or two of the above risk factors are eligible irrespective of the percentage of biopsy cores involved).

^bThe "untreated malignancy" section of the ACE-27 form is to be disregarded with respect to the patient's newly diagnosed, untreated prostate cancer.

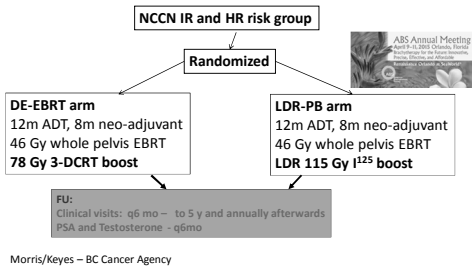
^{***}Patients with Gleason score ≥ 8, PSA > 20, or clinical stage > T2c are ineligible for this study.

My Recommendations for ADT and CV Risk:

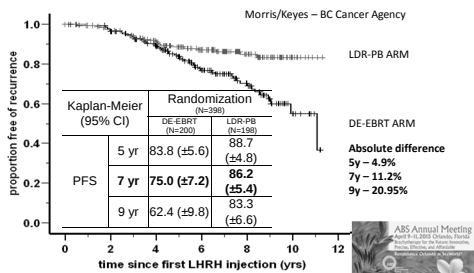
- Continue to use short-course ADT for patients w/unfavorable intermediate risk disease
- For favorable intermediate, rates of recurrence are low, and dose escalated radiation alone without ADT is reasonable for select cases
 - For unfavorable risk w/multiple comorbidities, a post-hoc analysis suggests they may not benefit from ADT, but until RTOG 08-15 is published, these patients should still receive ADT and should be medically optimized w/a cardiologist, monitored closely for diabetes and hyperlipidemia and encouraged to exercise.

Role of Brachytherapy Boost:
ASCENDE-RT

ASCENDE-RT



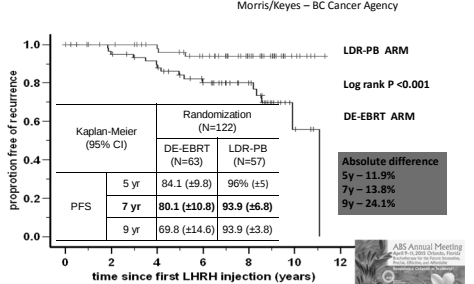
Results: Biochemical PFS
Intent-to-treat analysis of the primary endpoint



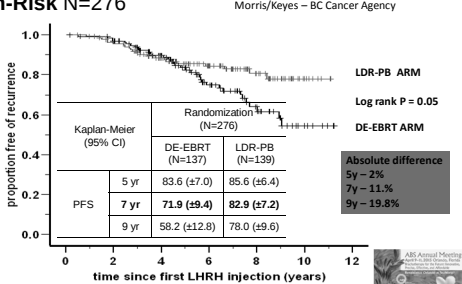
Risk Groups

- 68% NCCN High Risk
- 32% NCCN Intermediate Risk (most were unfavorable w/>50% PPC)

PFS by NCCN Risk Group
Intermediate-risk N=122



PFS by NCCN Risk Group
High-Risk N=276



ASCENDE-RT Considerations For Int Risk

Large Absolute Benefit in men with Intermediate Risk Disease (Mostly Unfavorable Intermediate): 94% vs. 70% PFS at 9 years

Increase in Urethral Strictures with Boost: 8% vs. 2%

No difference in survival yet

Worthwhile for younger, healthy men, with unfavorable intermediate risk disease

NCCN Unfavorable Intermediate Risk Generally adds short-course ADT to radiation

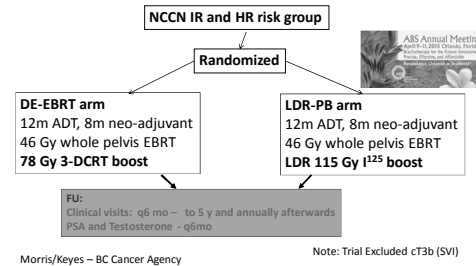
- RP
- EBRT + 4 to 6 months ADT
- EBRT + Brachy Boost (+/- 4 to 6 months ADT)

NCCN High Risk Adds Long-course ADT to radiation

- RP
- EBRT + 2 to 3 years ADT
- EBRT + Brachy Boost + 1 to 3 years ADT

- Note: 1 year duration was used in ASCENDE-RT trial, but the efficacy of this specific duration was never tested

ASCENDE-RT



What is the Optimal Duration of ADT?

Trials Showing Survival Benefits to Adding ADT to Radiation

Localized			Locally-Advanced	Node Positive
Low Risk	Interm Risk	High Risk		
	DFCI 95-096 6 months		EORTC 36 months	RTOG 85-31 Lifelong
	RTOG 94-08 4 months		*RTOG 92-02 DART 01/05 28 months	
		TROG 96.01 6 months		
		TROG 03*04 (RADAR) 18 months		

Summary: ADT Durations with RT

	Localized			Locally-Advanced	Node Positive
	Low Risk	Interm Risk	High Risk		
Standard	✗	4 mos		28-36 mos	Lifelong
		6 mos			
?			18 mos		2-3 yrs

NCCN Recommendation:
Long-Course ADT
(2-3 years) for
High Risk to Locally Advanced
Disease

RTOG 92-02 Horwitz (JCO 2008)

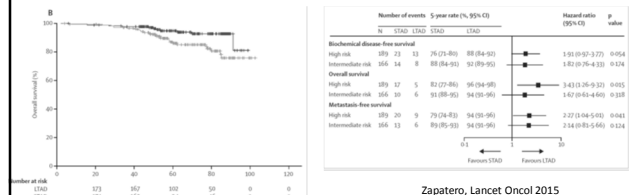
- cT2C – T4 and PSA < 150 (55% T3/4)
- 1554 pts. 65-70Gy + 4 vs. 28 mos ADT

28 mos improved 10-yr PC-specific survival (89 vs. 84%, $p=0.0042$)

OS improved only in a post-hoc analysis of Gleason 8-10 subgroup (45 vs. 32% $p=0.0061$)

DART 01/05 Trial (Lancet Oncol 2015) Redid RTOG 92-02 Using High Dose (78Gy) RT

- Essentially Same Results (28 mos improves OS Compared to 4 mos).
 No proven OS benefit in Intermediate Risk



EORTC Bolla (NEJM 2009)

- 77% T3 or T4, 6.3% N1
- 970 pts. 70Gy + 6 vs. 36 mos ADT

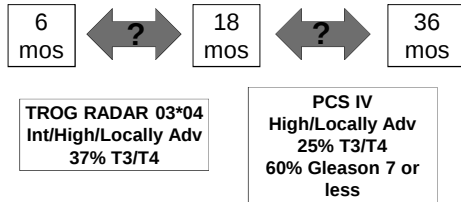
36 mos reduced 5-yr overall mortality by 3.8% (15.2% vs. 19.0%)

Long-Term ADT

Based on the EORTC, RTOG, and DART trials,
 2-3 years of ADT is considered the current
 standard of care for high risk/locally
 advanced patients

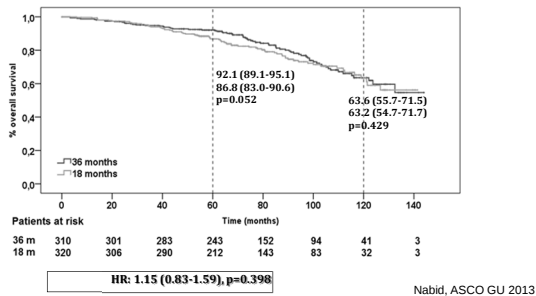
But what about 18 months?

18 Months: New Kid on the Block



PCS IV Nabid ASCO GU 2013

- Patients: 630 High Risk/Locally Adv
- Incl. criteria: T3/4 (25%) or PSA>20 (44%) or Gl 8-10 (40%)
- 70 Gy + 18 vs 36 months of ADT
 - Median f/u 77 months
- Biochem failure 25 vs. 19.4% (p=0.08)
- No signif difference in OS (HR 1.15, p=0.398)



Problems with 18 months in 2013

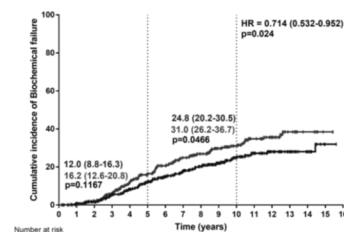
- PCS IV was not powered as an equivalence or non-inferiority study
- 18 months not proven to be equivalent or non-inferior to the standard 36 mos HR=1.15 (0.83-1.59) upper bound of 1.59 was too high to say non-inferior
- Needed more follow-up

ASCO 2017 Updates, Nabid et al

	ASCO GU 2013	ASCO 2017
Median f/u	6.4 years	9.4 years
Deaths	147	290
HR for All-Cause Mortality	1.15 [0.83-1.59]	1.02 [0.81-1.29]

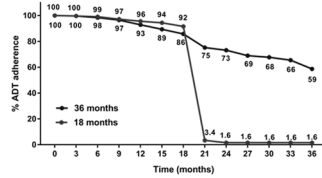
- Is an upper limit of 1.29 good enough?
 - Bolla NEJM 2009: 36 vs. 6 mos pre-set a 1.35 upper limit
 - Crook NEJM 2012: intermittent vs. continuous set a 1.25 upper limit

Biochemical Recurrence Worse w/18 months



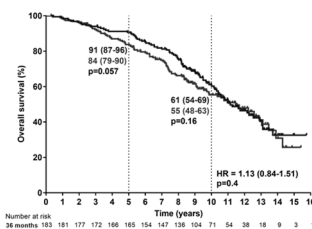
Compliance Was Poor in the 36 Month Arm

- 25% in the 36 month arm received 18 months or less, & only 59% received 36 months, which biases towards a null result.



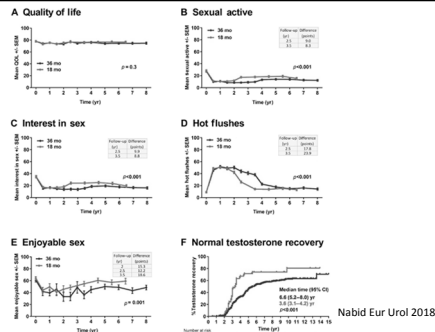
Result in Gleason 8-10 Group Not As Reassuring

A Overall Survival



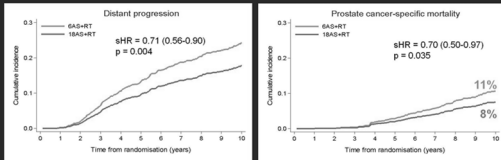
HR=1.13 (0.84 – 1.51) p=0.4, higher than HR of 1.02 for all patients, and 95% upper bound for Gleason 8-10 Overall Survival remains high

Overall QOL Same, but improvements in Sexual Function and Hot Flashes



TROG 03*04 (RADAR) Trial: 6 vs. 18 months ADT for Intermediate (34%) and High Risk (66%) Pca + RT (David Joseph, GU Cancers Symposium 2018)

Primary endpoint: PCSM



A 29% reduction in distant progression was the main driver of the 30% reduction in PCSM

Summary: ADT Durations with RT

	Localized			Locally-Advanced	Node Positive
	Low Risk	Interm Risk	High Risk		
Standard	✗	4 mos	28-36 mos		Lifelong
		6 mos			
?			18 mos		2-3 yrs

Additional Agents in the High-Risk Space?

- Docetaxel (Sandler)
 - RTOG 05-21: 4% improvement in OS at 4 years, but 2-sided p-value was 0.08 (1-sided=0.04) so not yet accepted widely
- Enzalutamide (Williams, Nguyen, Sweeney)
 - ENZARAD closed to accrual
- Apalutamide (Sandler)
 - ATLAS closed to accrual
- Abiraterone (James)
 - Reported

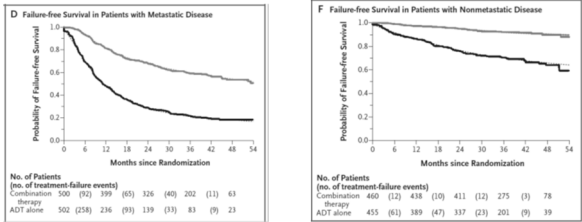
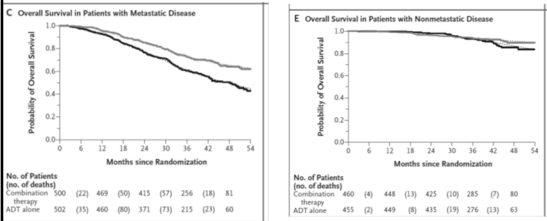
Abir:

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillissen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aug, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srichari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

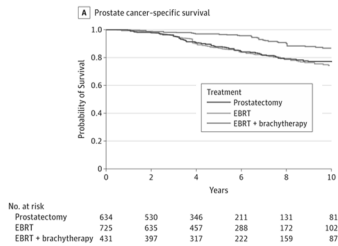


A Overall Survival	Subgroup	ADT Alone no. of deaths/no. of patients	Combination Therapy no. of deaths/no. of patients	Hazard Ratio with Combination Therapy (95% CI)	P Value for Interaction
	Metastatic status				0.37
	Nonmetastatic	44/455	34/460	0.75 (0.48–1.18)	
	Metastatic	218/502	150/500	0.61 (0.49–0.75)	0.80
	Nodal status				
	Negative	83/438	61/434	0.69 (0.49–0.96)	
	Positive	164/483	113/484	0.61 (0.48–0.77)	
	Indeterminate	15/16	10/42	0.68 (0.29–1.57)	0.57
	Gleason score				
	≤7	40/223	33/221	0.76 (0.48–1.23)	
	8–10	216/721	144/715	0.59 (0.48–0.73)	
	Unknown	6/13	7/24	0.47 (0.11–1.91)	0.003
	Age at randomization				
	<70 yr	180/596	110/603	0.51 (0.40–0.65)	
	≥70 yr	82/161	74/157	0.84 (0.69–1.29)	

Although there was no significant interaction between metastatic status and treatment effect, Abiraterone is not yet considered standard for high-risk prostate cancer getting radiation

How do Radiation and Surgery Compare for High Risk Disease?

Retrospective Data Conflicting: JAMA data Supporting Brachy Boost over RP in Gleason 9-10

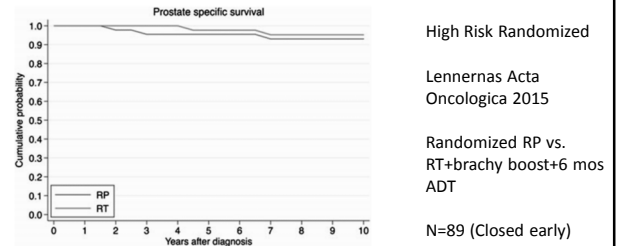


Gleason 9-10 non-randomized
Kishan JAMA 2018
RP vs RT vs RT+BT boost
Suggests BT boost is key

Retrospective Data Conflicting: Eur Urol Systematic Review of Retro Data Supporting RP over RT

- Wallis, et al Eur Urol 2016
- Systematic Review and Meta-Analysis of Observational Data
- HR for Overall Mortality RT vs. RP: 1.63 (1.54-1.73), $p < 0.00001$
- HR for PC-Mortality RT vs. RP: 2.08 (1.76 – 2.47) $p < 0.00001$

The only randomized trial of RP vs. RT for high risk Pca Showed Similar PCSM, but Underpowered



Summary: NCCN High Risk Adds Long-course ADT to radiation

- RP
 - EBRT + 2 to 3 years ADT
 - EBRT + Brachy Boost + 1 to 3 years ADT
- Note: 1 year duration was used in ASCENDE-RT trial, but the efficacy of this specific duration was never tested

Post-Operative Adjuvant and Salvage RT

ASTRO/AUA Guidelines

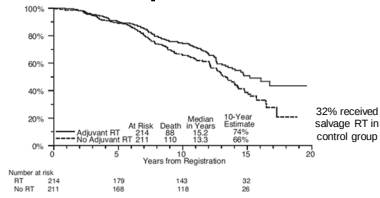
- Recommend Discussing and Potentially Offering Adjuvant Radiation to all patients with either:
 - Positive Margin
 - Pathologic T3 or higher Disease
- In current practice, fewer than 10% of patients with these features receive adjuvant RT nationwide.

3 RCTs Suggest Adjuvant RT Improves bRFS, But only 1 Showed OS Benefit

	Inclusion Criteria	%PSA<0.2 at entry	flu yrs	HR for bRFS	OS Benefit
SWOG 8794 Thompson	pT3 or +margin	66%	12.6	0.43	YES
EORTC 22911 Bolla	pT3 or +margin	70%	10.3	0.48	No
ARO 96-02 Wiegel	pT3	100%	9.2	0.53	No

Adjuvant RT cuts the risk of PSA recurrence by about 50%

SWOG Trial: Only Trial that Showed Adjuvant RT Improved OS



But, only 32% in control arm got salvage RT, and it was initiated too late (when PSA =1.0 median), and 33% had detectable PSA at Entry
Not a Trial of Adjuvant vs. Modern Day Close Observation with Early Salvage

Long-Term Toxicity Tolerable

	Incontinence	Stricture	Rectal
SWOG 8794 "Thompson"	6% vs 3% (p=0.11)	18% vs 9% (p=0.02)	3.3% vs. 0% (p=0.02)
EORTC 22911 "Bolla"	23% vs 17% (p=NS) (any leakage)	NR	NR
ARO 96-02 "German"	Not assessed	1 in each arm	1.4% vs 0%

Den, JCO 2015: Genomic Classifier May Identify Men Who Benefit Most from Adjuvant RT

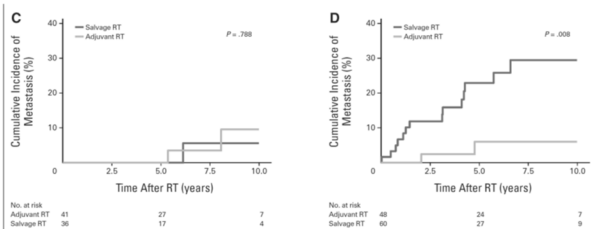


Fig 3. Cumulative incidence curves to evaluate benefit from adjuvant radiotherapy (RT) versus salvage RT stratified by (A and B) Cancer of the Prostate Risk Assessment Postoperative (CAPRA-Si) score and (C and D) genomic classifier (GC).

Risk-Adapted Approach May be Most Sensible

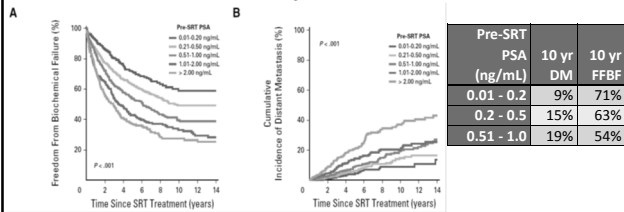
- I consider adjuvant for young patients with the highest absolute risk of recurrence, as they will have the highest absolute benefit from a 50% relative reduction in recurrence
- Note that 40% with pT3 or positive margin remain disease-free on observation alone through 10 years (Bolla EORTC Trial)
- Genomic Testing May also Help Identify Patients who Benefit Most from Adjuvant RT

RADICALS, RAVES, and EORTC Trial Seek to Answer the Adjuvant vs. Early Salvage Question

- RADICALS:
 - 2x2 Trial of Adjuvant vs. Early Salvage Radiation at PSA >0.2
 - And 0 vs. 6 vs. 24 months of ADT
- RAVES:
 - Adjuvant vs. Early Salvage Radiation at PSA >0.2
- EORTC:
 - Adjuvant vs. Early Salvage Radiation at PSA >0.1

Salvage RT + ADT

Tendulkar JCO 2016 – Initiation of Salvage RT at Lower PSA May Reduce Metastases



RTOG 96-01: Survival Benefit to Adding ADT to Salvage RT

13-year follow-up

- Rising PSA after RP (pT3 or pT2R1), N=771
 - Median PSA at entry was 0.6
- Salvage RT +/- 2 years bicalutamide 150mg

10-year	RT	RT+ADT	HR	P-value
Metastasis	19%	11%	0.63	P<0.01
PCSM	10.1%	4.5%	0.49	P<0.001
OS	78%	82%	0.77	P=0.036

GU Cancers Symposium, 2016
NEJM, 2017

The Case for ADT Today

- Proven Overall Survival Benefit
- Reasonable number needed to treat ratios

Outcome	Absolute Benefit at 10 years	Number Needed to Treat
Metastasis	8%	12
PCSM	5.6%	18
Overall Mortality	4%	25

GETUG/AFU-16 – No survival benefit (yet)

- N=743
- Rising PSA after RP
- Salvage RT +/- 6 mos goserelin

5-year	RT	RT+ADT	P-value
bRFS	62.1%	79.6%	P<0.001
OS	94.8%	96.2%	P=0.18

Lancet Oncology, 2017

Why 6 months GnRH agonist may be Enough

	RTOG 96-01	GETUG-16
	2 yrs bicalutamide	6 mos goserelin
bRFS HR	0.48 (p<0.001)	0.50 (p<0.0001)
OS HR	0.77 (p=0.04)	0.70 (p=0.18)
Median FU	13 years	5 years

Case Against ADT: Subgroup Analyses

- PSA <0.7: No benefit to ADT
- PSA 0.7-1.5: Moderate benefit to ADT
- PSA >1.5: Larger Benefit to ADT

Don't most patients getting salvage XRT today have a PSA less than 0.7??

Note this 0.7 cutoff was not pre-stratified (Only PSA >1.5 was pre-stratified)

Subgroups of 96-01: Forest Plots for OS

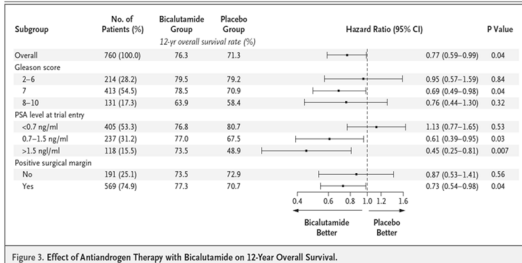


Figure 3. Effect of Antiandrogen Therapy with Bicalutamide on 12-Year Overall Survival.

Shipley NEJM 2017

Subgroup Analysis for Distant Metastasis

Table 2. Antitumor Efficacy with Respect to Key Secondary End Points at 12 Years.

End Point and Subgroup	Bicalutamide Group		Placebo Group		Hazard Ratio (95% CI)	P Value
	Patients at Risk no.	Rate of End Point %	Patients at Risk no.	Rate of End Point %		
Metastatic prostate cancer						
All patients	384	14.5	376	23.0	0.63 (0.46-0.87)	0.005
Gleason score						
2-6	111	7.8	103	16.5	0.64 (0.30-1.36)	0.25
7	205	15.4	208	19.8	0.80 (0.52-1.22)	0.31
8-10	67	21.2	64	44.7	0.35 (0.18-0.67)	0.001
PSA level at trial entry						
<0.7 ng/ml	210	13.4	195	17.1	0.76 (0.47-1.22)	0.26
0.7-1.5 ng/ml	119	17.4	118	28.4	0.67 (0.40-1.12)	0.13
>1.5 ng/ml	55	13.1	63	31.1	0.36 (0.15-0.84)	0.01
Positive surgical margin						

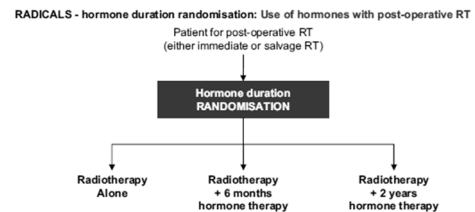
Shipley NEJM 2017

Which patients can avoid ADT?

The PSA <0.7 was an unplanned subgroup analysis, so cannot have complete confidence in this, but...

For PSA<0.5 w/positive margins, Gleason<= 3+4=7, pT2, absolute benefit of ADT on OS likely small, especially if older

RADICALS Will Give More Info



NRG GU-006 (PI – Dan Spratt)

- Randomized Phase II Trial Focused on Patients with more favorable risk getting salvage radiation
 - Biomarker Stratified by PAM 50
 - Randomized to Radiation vs. Radiation + Apalutamide
- NCT03371719

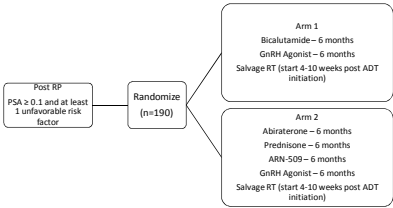
FORMULA-509: Facilitation of Radiation Management Using Lupron, Abiraterone, and ARN-509



NCT03141671, PI: NGUYEN (DFCI), SPRATT (MICH), HOFFMAN

(MDACC), KOLLMEIER (MSKCC), LIAUW (U CHICAGO)

Schema



Summary Post-Op

- Risk-Adapted Consideration of Adjuvant RT for Young Margin Positive or pT3 Patients with Highest Absolute Risk of Recurrence
- For Most Others, Close Observation and Early Initiation of Salvage Radiation when PSA Rises to 0.1 or 0.2 May Yield Similar Survival and Spare 40% of Men from Radiation
- Salvage Radiation Typically Should be Accompanied by 6 months of GnRH-based ADT (or less commonly 2 yrs bicalutamide)
- Some controversy as to whether patients with PSA <0.7 at salvage have enough benefit from ADT with salvage RT

Thank you!



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Patient-Reported Outcomes After Localized Prostate Cancer Treatments

Peter Chang, MD, MPH
 Director, Prostate Cancer Center, BIDMC
 Martin and Diane Trust Career Development Chair in Surgery
 Assistant Professor of Surgery

Comprehensive Review of Urology
2018

Disclosures

- None



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Overview

- Patient-Reported Outcomes - Definitions
- History/Rationale
- Instruments
- Interpreting and Using Patient-Reported Outcomes



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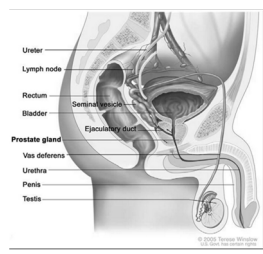


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Prostate Cancer – The Treatment Conundrum

- Long-term survival
 - 100% survival at 5 years if localized or regional
 - 10 year survival: 99%. 15-year survival: 94%
 - 28% survival at 5 years if distant metastases on presentation
- Long-term consequences
 - Treatment can affect health-related quality of life (HRQOL) in multiple domains





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How do we assess the side effects of treatment?

- **Physician-reported outcomes**
 - We "take a history"
 - We use patient responses to make professional assessment or judgment of the patient's condition
 - *The patient is doing very well from a urinary standpoint – minimal incontinence, rarely leaks*
 - *"The patient has no issues with sexual function"*
 - *"The patient is satisfied with his urinary control and does not desire further treatment"*



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What are patient-reported outcomes (PROs)?

- **PRO**: a questionnaire used in a clinical trial or in a clinical setting where the responses are collected **directly from the patient**
 - The **patient** provides the information
 - Questionnaires or interviews*
 - Interviewer is gaining and documenting patient's view based on set questions, not interpreting and assessing patient's views



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Outcomes: Ask the patient, not the doctor

- Sexual function: % of patients that had erections firm enough for intercourse in the month preceding interview
 - Fowler et al: 10%
 - Most recent review of literature at the time: 40%
- Urinary function: % of patients that reported problems with leakage/wetness
 - Fowler et al: 60%
 - Literature review: 27%

PATIENT-REPORTED COMPLICATIONS AND FOLLOW-UP TREATMENT AFTER RADICAL PROSTATECTOMY

The National Medicare Experience: 1988–1990* (Updated June 1993)

FLOYD J. FOWLER, Jr., Ph.D.
MICHAEL J. BARRE, M.D.
GRACE LU-YAO, Ph.D.

ANTHONY ROMAN, M.A.
JOHN WASSON, M.D.
JOHN E. WENNBERG, M.D.

From the Center for Survey Research, University of Massachusetts, the Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, Massachusetts, and the Center for the Evaluative Clinical Sciences, Dartmouth Medical School, Hanover, New Hampshire



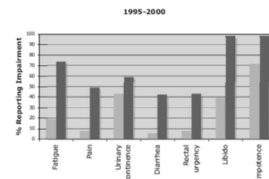
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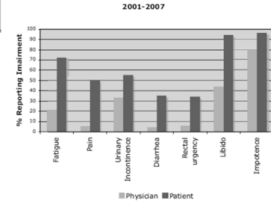


Physician-reported vs Patient-reported outcomes: Physicians tend to underestimate patients' symptoms



Red bars: QOL problems from patient perspective

Blue bars: QOL problems from physician perspective



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Sonn GA, Sridharan N, Piantadosi JC, et al. Differing perceptions of quality of life in patients with prostate cancer and their doctors. J Urol 2009; 182: 2296.



Model Example in Urology: The AUA Symptom Index

The AUA-Symptom Index (IPSS)

- Developed to objectively document symptom severity in men with LUTS
- Easily scored
- Used as an outcome measure in RCTs
- Can predict clinical outcome (retention, need for TURP, etc)

	None at all	Seldom	Sometimes	Often	Always
1. Frequency/Emptying How often do you urinate, and how often do you feel you need to urinate?	0	1	2	3	4
2. Urgency How often do you feel you need to urinate so soon that you may not get to the bathroom in time?	0	1	2	3	4
3. Intermittency How often do you have trouble getting started when you want to urinate?	0	1	2	3	4
4. Urgency How often do you have to urinate so soon that you may not get to the bathroom in time?	0	1	2	3	4
5. Weak Stream How often do you have trouble getting started when you want to urinate?	0	1	2	3	4
6. Nocturia How often do you wake up at night to urinate?	0	1	2	3	4
7. Nocturia How often do you wake up at night to urinate?	0	1	2	3	4
Total IPSS Score					



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Function and Bother

- Function – objective measurement of a health state or question
- Bother – inherently subjective measurement of a combination of patient satisfaction and discomfort with the disease and/or treatment

	None	1 time	2 times	3 times	4 times	5 times or more
7. Nocturia Over the past month, how many times did you most frequently get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5
Total IPSS Score						

	Dislighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
Quality of Life Due to Urinary Symptoms If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6



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Sexual Health Inventory for Men (SHIM)

OVER THE PAST 6 MONTHS:

	Very Low	Low	Moderate	High	Very High
1. How do you rate your confidence that you could get and keep an erection?	1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	0	1	2	3	4
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0	1	2	3	4
4. During sexual intercourse, how often were you able to maintain your erection to completion of intercourse?	0	1	2	3	4
5. When you attempted sexual intercourse, how often was it satisfactory for you?	0	1	2	3	4

Add the numbers corresponding to questions 1-5. TOTAL: The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints: 1-7 Severe ED, 8-11 Moderate ED, 12-16 Mild to Moderate ED, 17-21 Mild ED



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PROs in prostate cancer

- Urology at forefront of disease-specific PRO development
 - UCLA-Prostate Cancer Index (UCLA-PCI)
 - Expanded Prostate Cancer Index Composite (EPIC)
 - EPIC-50
 - EPIC-26
 - EPIC-CP
 - Others (EORTC QLQ-C30, MSKCC STAR)



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UCLA-Prostate Cancer Index (UCLA-PCI)

- Developed by Mark Litwin et al in 1995
- Construct validity – are the questions relevant and representative of the construct (prostate cancer)?
- Multi-step, iterative process
 - Patient focus groups
 - Psychometric assessment and validation
- Identified health domains affected by prostate cancer treatment
- Measured function and bother

Urinary (incontinence)	Sexual	Bowel
Function (5)	Function (8)	Function (4)
Bother (1)	Bother (1)	Bother (1)



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Litwin MS, Hays RD, Fink A, Ganz PA, Leake R, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care. 1998 Jul;36(7):1002-12.

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Expanded Prostate Cancer Index Composite

- Developed by Wei and Sanda et al in 2000
- Health Domain Expansion to capture effects of a broader array of treatments (brachytherapy, hormonal therapy)
 - Urinary incontinence
 - Urinary irritation/obstruction
 - Bowel
 - Sexual
 - Vitality/Hormonal
- 50 items total
- Kept both items from UCLA-PCI



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Wei JT, Dunn RL, Litwin MS, et al. Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56:889-905.

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EPIC-26 (also known as EPIC-Short Form)

The following questions are about urinary, bowel, sexual, and hormonal control.

Over the PAST 4 WEEKS, how often have you leaked urine?

More than once a day
About once a day
More than once a week
About once a week
Rarely or never

Which of the following best describes your urinary control DURING THE LAST 4 WEEKS? (Please select only one)

No urinary control
Frequent dribbling
Total control

How many pads or adult diapers did you use to control leakage DURING THE LAST 4 WEEKS? (Please select only one)

None
One pad per day
Two pads per day
Three or more pads per day

How big a problem, if any, has each of the following been for you DURING THE LAST 4 WEEKS? (Please select only one)

Dribbling or leaking urine
Pain or burning on urination
Bleeding with urination
Weak urine stream or incomplete emptying
Need to urinate frequently

Overall, how big a problem has your urinary function been for you DURING THE LAST 4 WEEKS? (Please select only one)

No Problem
Very Small Problem
Small Problem
Moderate Problem
Big Problem

How big a problem, if any, has each of the following been for you? (Please select only one)

Urgency to have a bowel movement
Increased frequency of bowel movements
Losing control of your stools
Bloody stools
Abdominal/Rectal pain

Overall, how big a problem have your bowel habits been for you DURING THE LAST 4 WEEKS? (Please select only one)

No Problem
Very Small Problem
Small Problem
Moderate Problem
Big Problem

How would you rate each of the following DURING THE LAST 4 WEEKS? (Please select only one)

Your ability to have an erection
Your ability to reach orgasm (climax)
How would you describe the usual QUALITY of your erections DURING THE LAST 4 WEEKS?
None at all
Not firm enough for any sexual activity
Firm enough for masturbation and foreplay only
Firm enough for intercourse

How would you describe the FREQUENCY of your erections DURING THE LAST 4 WEEKS? (Please select only one)

NEVER had an erection when I wanted one
I had an erection LESS THAN HALF the time I wanted one
I had an erection ABOUT HALF the time I wanted one
I had an erection MORE THAN HALF the time I wanted one
I had an erection WHENEVER I wanted one

Overall, how would you rate your ability to function sexually DURING THE LAST 4 WEEKS? (Please select only one)

Very poor
Poor
Fair
Good
Very good

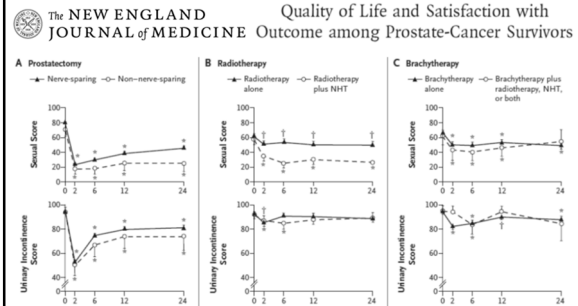
Overall, how big a problem has your sexual function or lack of sexual function been for you DURING THE LAST 4 WEEKS? (Please select only one)

No Problem
Very Small Problem
Small Problem
Moderate Problem
Big Problem

How big a problem DURING THE LAST 4 WEEKS, if any, has each of the following been for you? (Please select only one)

Hot flashes
Breast tenderness/enlargement
Feeling depressed
Lack of energy
Change in body weight

Treatment Results Revealed by Patient-Reported Outcomes



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Sanda MG, Dunn RL, Michalski J, et al. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. NEJM. 2008;358:1250-61.

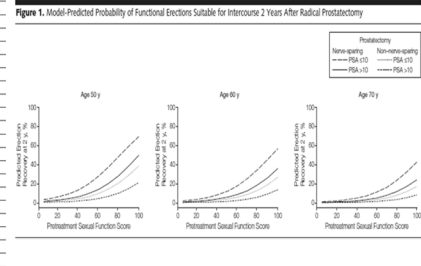
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Quality-of-Life Domain and EPIC Questionnaire Item	Prostatectomy					External-Beam Radiotherapy					Brachytherapy				
	Baseline (N=603)	2 Mo (N=573)	6 Mo (N=573)	12 Mo (N=573)	24 Mo (N=573)	Baseline (N=292)	2 Mo (N=276)	6 Mo (N=264)	12 Mo (N=258)	24 Mo (N=178)	Baseline (N=306)	2 Mo (N=286)	6 Mo (N=288)	12 Mo (N=272)	24 Mo (N=186)
Urinary function															
Initiation or obstruction†															
Dysuria	1	7	1	1	<1	1	12	5	1	1	1	24	11	11	5
Hematuria	<1	1	<1	<1	0	1	<1	2	1	1	<1	1	<1	1	1
Weak stream	12	12	6	3	4	13	23	11	12	10	7	40	26	18	11
Frequency	17	24	14	11	10	16	14	19	13	14	11	45	31	20	20
Incontinence															
Leaking >1 time per day	4	52	23	16	14	6	15	9	8	7	5	13	9	6	10
Frequent dribbling	2	20	6	4	5	2	6	2	3	2	<1	8	5	3	3
Any pad use	1	87	34	24	10	1	4	6	3	5	2	9	6	7	8
Leaking problem‡	2	30	9	8	8	2	6	6	4	5	1	6	7	4	6
Overall urinary problem§	11	29	10	7	7	11	30	12	11	11	8	39	25	18	16
Bowel function															
Urgency	1	5	3	3	2	3	18	12	14	16	4	19	14	10	9
Frequency	1	3	2	1	<1	2	16	9	9	10	3	17	9	8	7
Rectal incontinence	<1	1	1	<1	<1	<1	5	4	4	2	<1	6	6	4	4
Bloody stools	<1	<1	1	<1	<1	1	3	1	5	5	<1	1	2	3	3
Rectal pain	1	4	3	2	2	2	7	5	3	4	2	10	5	4	5
Overall bowel problem	1	3	3	2	1	3	16	9	9	11	2	15	12	9	8
Sexual function															
Poor erections	14	88	80	67	58	37	52	56	57	60	30	51	50	48	51
Difficulty with orgasm	12	62	51	45	42	32	47	53	52	50	24	49	44	38	45
Erections not firm¶	17	90	84	74	64	64	48	63	62	64	36	58	58	54	56
Erections not reliable¶	20	83	75	66	51	39	46	48	51	51	24	42	47	40	44
Poor sexual function	12	83	74	61	53	34	50	54	53	58	28	47	48	43	46
Overall sexual problem	12	59	59	50	43	18	28	30	29	37	18	34	34	29	30
Vitality or hormonal function††															
Hot flashes	<1	2	4	4	4	1	11	12	8	3	1	3	4	1	2
Breast problems	0	0	<1	1	1	1	2	2	2	2	1	1	1	1	1
Depression	9	6	7	6	7	4	5	5	8	4	4	8	5	4	4
Lack of energy	9	11	10	10	12	12	23	21	19	16	7	21	17	14	12
Weight change	4	5	5	6	5	4	5	7	7	7	3	7	7	8	6

JAMA®

The Journal of the American Medical Association
September 21, 2011

Prediction of Erectile Function Following Treatment for Prostate Cancer



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Almouzar M, Begen MM, Goepferberg MR, et al. Personalized prediction of erection recovery after primary prostate cancer treatment: validation in the community-based CAPSIRE cohort of a predictive model developed in PROST-QA. JAMA. 2011; Sep 21;306(12):1260-14.

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JAMA
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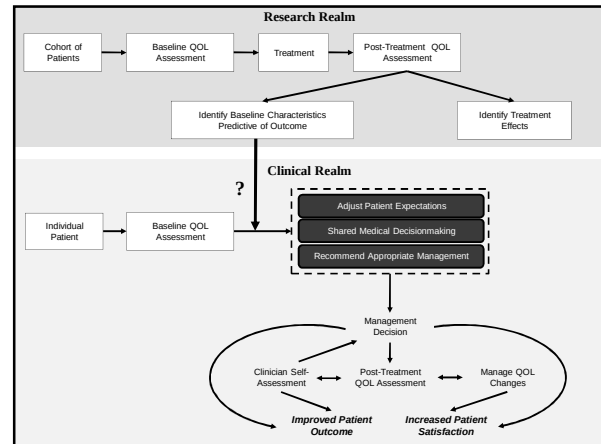
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Rodney L. Dunn, MS
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Martin G. Sandoz, MD

Prediction of Erectile Function Following Treatment for Prostate Cancer

Table 2. PROSTQA Model–Predicted Probabilities of Men Having Functional Erections Suitable for Intercourse 2 Years After Radical Prostatectomy

Planned Surgical Technique	Patient Age, y	Pretreatment PSA Level, ng/mL	Predicted Functional Erections After Treatment, % (95% CI) (by Pretreatment Sexual HRQOL Score) ^{a,b}			
			67	83	100	
Nerve-sparing	≤10	35 (25–45)	52 (43–61)	70 (61–77)		
	>10	18 (9–34)	32 (18–49)	50 (33–68)		
	60	≤10	23 (18–30)	38 (33–44)	57 (49–64)	
	>10	11 (3–21)	21 (12–34)	36 (22–53)		
	70	≤10	15 (10–22)	26 (19–35)	43 (32–55)	
	>10	7 (3–14)	13 (7–24)	24 (13–41)		
Non-nerve-sparing	≤10	13 (5–30)	23 (9–46)	30 (18–46)		
	>10	6 (2–18)	11 (4–31)	21 (7–48)		
	60	≤10	8 (3–19)	14 (6–32)	27 (12–50)	
	>10	3 (1–11)	7 (2–19)	13 (4–34)		
	70	≤10	5 (2–12)	9 (3–22)	17 (7–37)	
	>10	2 (1–7)	4 (1–12)	8 (3–22)		

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The Problem with Most Prostate Cancer PROs

- PCa PROs too difficult to use in practice
- Existing HRQOL patient-reported instruments (UCLA-PCI, EPIC) are too difficult to use in routine practice
 - Lengthy: 3-5 pages
 - Time: >10-15 minutes
 - Scoring: transformation of scores to 0-100

Step 1. RECODING ITEMS

Item Number	Change original response category from	To recoded value of
12,13,19,23	1	0
	2	33
	3	67
	4	100
14,26	1	0
	2	50
	3	100

Step 2. AVERAGING RECODED ITEMS INTO SCALES

Scale	Number/Scale of Items	Average the following recoded items
Urinary function	4	12,13,14,19,23
Bowel function	4	17,18,19,20
Sexual function	8	2,9,20,25,27,32,33,35,37
Urinary bother	1	10
Bowel bother	1	21
Sexual bother	1	25

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Modifying PRO instruments for Clinical Practice

- Developed and validated a version of EPIC suitable for use in routine clinical practice at the **point-of-care**
- EPIC for Clinical Practice (EPIC-CP): Design criteria
 - Practical and convenient
 - Easier patient completion (shorter, faster)
 - Easier clinician interpretation (revised scoring system)
 - Valid and useful
 - Psychometrically sound
 - Sensitive to treatment effect

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EPIC-CP Design

- Reduction of EPIC-26**
 - 3 questions per HRQOL domain
 - Keep overall bother questions from UCLA-PCI/EPIC
 - Clinically prevalent and useful questions

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EPIC-CP Design

- Scoring System Redesign**
 - Analogous to AUA-Symptom Index and SHIM
 - Add question answers to calculate domain scores
 - Each question scored from 0 to 4
 - Each domain scored from 0 to 12 (3 questions/domain)

	UCLA-PCI and EPIC-50/26	EPIC-CP
Score range in each domain	0 – 100	0 - 12
Better QOL	Higher score	Lower score

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EPIC for Clinical Practice (EPIC-CP)

Validation: Chang P et al J Urol Sep 2011

■ **WHY:** For use in clinical practice

■ **WHO:** Any prostate cancer patient

■ **LENGTH:** 1 page, 16 questions

■ **COMPLETION TIME:** < 5 minutes

■ **SCORING:** Similar to AUA-SI/IPSS

■ **WHAT DOES IT MEASURE:**

- Urinary incontinence
- Urinary irritation/obstruction
- Bowel/Rectal
- Sexual
- Vitality/Hormonal

■ **FREELY AVAILABLE:**
<http://www.bidmc.org/epic>
 Free full text through Pubmed

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Expanded Prostate Cancer Index Composite for Clinical Practice: Development and Validation of a Practical Health Related Quality of Life Instrument for Use in the Routine Clinical Care of Patients With Prostate Cancer

Peter Chang, Konrad M. Szymanski, Rodney L. Dunn, Jonathan J. Chipman, Mark S. Litwin, Paul L. Nguyen, Christopher J. Sweeney, Robert Cook, Andrew A. Wagner, William C. DeWolf, Glenn J. Bubley, Renee Funches, Joseph A. Aronovitz, John T. Wei* and Martin G. Sanda*,†,‡

- Psychometrically sound (Cronbach's alpha > 0.70)
- All domains correlate highly (>0.9) with EPIC-26/50
- Sensitive to treatment effects
- Practical for clinical practice
 - 77% of patients completed in < 5 min, 96% in <10 min
 - 87% of clinicians found EPIC-CP very convenient to use in the flow of routine clinical practice

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Table 2. Correlation between individual items and total scores for EPIC-26 and EPIC-CP, and correlation of domain summary scores of EPIC-CP with previous versions of EPIC

Quality of Life Domain + Individual EPIC-CP Questionnaire Item	Item No.		Item-Scale Correlation		Domain Score Correlations of EPIC-CP With Previous Versions of EPIC	
	EPIC-26	EPIC-CP	EPIC-26	EPIC-CP	EPIC-50	EPIC-26
Urinary domains:						
Overall urinary problem (1)*	5	1	Not applicable	Not applicable	0.96	0.96
Incontinence subscale (3):						
Frequent dribbling*	2	2	0.77	0.75		
Any pad use*	3	3	0.86	0.86		
Leaking problem*	4a	4	0.83	0.76		
Irritation/obstruction subscale (3):					0.98	0.97
Dysuria†	4b	5a	0.65	0.61		
Weak stream†	4d	5b	0.67	0.69		
Frequency†	4e	5c	0.61	0.62		
Bowel domain (3):					0.97	0.94
Urgency or rectal pain	6a/6e	6a	0.77/0.65	0.81		
Frequency†	6b	6b	0.81	0.80		
Overall bowel problem*	7	6c	0.83	0.77		
Sexual domain (3):					0.95	0.93
Difficulty with orgasm*	8b	7	0.68	0.63		
Erections not firm*	9	8	0.79	0.62		
Overall sexuality problem*	12	9	0.50	0.35		
Vitality or hormonal domain (3):					0.97	0.94
Hot flashes or breast problems†	13a/13b	10a	0.38/0.31	0.29		
Depression†	13c	10b	0.62	0.60		
Lack of energy†	13d	10c	0.58	0.62		

* These 8 items (1, 2, 3, 4, 6c, 7, 8, 9) were original UCLA-PCI items retained for generalizability and clinically significant assessment. Item 5 in the EPIC-26 and item 1 in EPIC-CP are the UCLA urinary bother item; because this item related to incontinence and irritative/obstructive scale in factor analyses and conceptual content, it was not included in the irritative/obstructive or urinary incontinence scale, but was retained to enable assessment of overall urinary bother, which could be influenced by either or both of these domains.

† Items retained from the EPIC-50 and EPIC-26.

‡ Two items from the EPIC-26 were combined to preserve conceptual content in the EPIC-CP.

Internal consistency validity

- Do the questions within health domains group together and measure a concept, or are they disparate, measuring different things?
- Cronbach's alpha coefficient
 - Considered acceptable to be > 0.70

Table 3. Domain characteristics of EPIC-CP in 175 subjects treated for prostate cancer in the EPIC-CP validation cohort

	Mean (SD)	Median (IQR)	Range	% Scoring Min	% Scoring Max	Cronbach's α (95% CI)*
Urinary:						
Incontinence	1.76 (2.27)	1.0 (0.0-3.0)	0.0-11.0	42.2	0.0	0.81 (0.77-0.86)
Irritation/obstruction	2.79 (2.62)	2.0 (1.0-4.0)	0.0-12.0	19.0	1.1	0.72 (0.63-0.77)
Bowel	1.65 (2.48)	0.0 (0.0-2.0)	0.0-11.0	51.4	0.0	0.84 (0.78-0.88)
Sexual	6.47 (3.92)	7.0 (3.0-9.5)	0.0-12.0	8.8	12.6	0.80 (0.74-0.84)
Vitality/hormonal	2.43 (2.57)	2.0 (0.0-4.0)	0.0-11.0	29.9	0.0	0.64 (0.54-0.73)

Domain summary scores range from 0 (best possible score) to 12 (worst possible score).

* Estimated from 500 bootstrap samples.

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EPIC-CP is sensitive to treatment effects on HRQOL

Table 4. Sensitivity of the EPIC-CP to HRQOL differences associated with prostate cancer treatment

HRQOL Domain*	Any			p Value†
	Treatment	Active Surveillance	Untreated	
No. pts	175	32	132	
Mean urinary (SD):				
Overall urinary bother	1.32 (1.29)	1.25 (1.32)	1.11 (1.17)	0.14
Incontinence	1.76 (2.27)	0.87 (1.41)	1.06 (1.85)	0.004
Irritation/obstruction	2.79 (2.62)	2.28 (2.22)	2.16 (1.99)	0.02
Mean bowel (SD)	1.65 (2.48)	0.94 (1.63)	1.11 (1.88)	0.04
Mean sexual (SD)	6.47 (3.92)	4.16 (3.12)	3.73 (3.20)	<0.0001
Mean vitality/hormonal (SD)	2.43 (2.57)	1.88 (2.14)	1.92 (2.38)	0.08
Overall scores	14.66 (9.00)	9.77 (7.40)	9.59 (7.75)	<0.0001

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EPIC-CP is suitable and convenient to use in practice

Table 5. Ease of using EPIC-CP in routine clinical practice

	%
Mins for pt to fill out EPIC-CP:	
Less than 5	77
5-10	19
10-15	2
Greater than 15	Less than 1
Convenience of EPIC-CP administration in routine clinical practice by clinician:	
Very convenient	87
Somewhat convenient	12
Somewhat inconvenient	Less than 1
Very inconvenient	0
Pt completed all questions	89

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Measuring and Predicting Prostate Cancer Related Quality of Life Changes Using EPIC for Clinical Practice

Jonathan J. Chipman, Martin G. Sanda, Rodney L. Dunn, John T. Wei, Mark S. Litwin, Catrina M. Crociani, Meredith M. Regan, Peter Chang* and the PROST-QA Consortium

- Further validation and characterization of EPIC-CP using the PROST-QA cohort
- Objectives:
 - Assess the ability of EPIC-CP to detect treatment-related changes over time
 - Apply EPIC-CP to render an existing multivariable PROST-QA predictive model usable at the point of care
 - Determine what constitutes a clinically meaningful change in EPIC-26 and EPIC-CP score



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Chipman J et al J Urol Mar 2014

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EPIC-CP: Responsive to HRQOL changes over time

Table 2. Domain specific short-term and long-term changes in EPIC-CP scores from pretreatment baseline by treatment group in 3 of 6 groups analyzed

	Mean ± SE Baseline	Mean ± SE Short Term	Mean ± SE Long Term
Nerve sparing radical prostatectomy:			
Urinary incontinence	0.5 ± 0.0	4.2 ± 0.1*	1.6 ± 0.1*
Urinary irritation/obstruction	2.0 ± 0.1	2.6 ± 0.1†	1.2 ± 0.1†
Bowel	0.7 ± 0.1	1.2 ± 0.1†	0.8 ± 0.1†
Sexual	2.1 ± 0.1	8.0 ± 0.1*	5.8 ± 0.2*
Vitality/homonal	1.4 ± 0.1	1.6 ± 0.1†	1.3 ± 0.1†
External beam radiotherapy + neoadjuvant hormonal therapy:			
Urinary incontinence	0.6 ± 0.1	1.1 ± 0.2†	0.9 ± 0.2
Urinary irritation/obstruction	1.8 ± 0.2	3.2 ± 0.3*	1.9 ± 0.3†
Bowel	0.8 ± 0.2	2.8 ± 0.4*	2.2 ± 0.4*
Sexual	4.4 ± 0.4	8.1 ± 0.4*	7.2 ± 0.4*
Vitality/homonal	1.2 ± 0.2	3.7 ± 0.3*	2.0 ± 0.3†
Brachytherapy alone:			
Urinary incontinence	0.5 ± 0.1	1.6 ± 0.1*	1.1 ± 0.1*
Urinary irritation/obstruction	1.6 ± 0.1	5.7 ± 0.2*	2.6 ± 0.2†
Bowel	0.7 ± 0.1	3.4 ± 0.2*	1.8 ± 0.2*
Sexual	3.4 ± 0.2	5.3 ± 0.2*	5.3 ± 0.2*
Vitality/homonal	1.1 ± 0.1	1.9 ± 0.1†	1.3 ± 0.1†

*HRQOL statistically and clinically significantly different from pretreatment baseline.
†HRQOL statistically significantly different from pretreatment baseline only.



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EPIC-CP: Defining the MID

- Domain summary scores can be difficult to interpret
- What change in score is clinically relevant?
- "Minimally important difference"
- Also called "clinically significant change"
- Distribution** and anchor-based approaches

Table 3. EPIC-CP minimally important differences

	MID (treatment group range)
Urinary incontinence	1.0 (0.7–1.5)
Urinary irritation/obstruction	1.3 (1.1–1.4)
Bowel	1.2 (0.9–1.5)
Sexual	1.6 (1.4–1.9)
Vitality/homonal	1.0 (0.9–1.3)



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Table 4. Multivariable nomogram predicting probability of functional erection 2 years after radical prostatectomy based on pretreatment EPIC-CP and EPIC-26 sexual scores by planned surgical technique

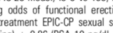
Age (ng/dl pretreatment PSA)	EPIC-CP Score ^{a,†}			EPIC-26 Score ^{a,‡}		
	0	2	4	100	83	67
Nerve sparing						
50:						
10 or Less	67	30	34	70	32	35
Greater than 10	46	50	18	50	52	18
60:						
10 or Less	53	36	22	57	38	23
Greater than 10	32	19	11	36	21	11
70:						
10 or Less	39	24	14	43	26	15
Greater than 10	21	12	6	24	13	7
Nonnerve sparing						
50:						
10 or Less	35	21	12	39	23	13
Greater than 10	19	10	6	21	11	6
60:						
10 or Less	23	13	7	27	15	8
Greater than 10	11	6	3	13	7	3
70:						
10 or Less	15	8	4	17	9	5
Greater than 10	7	3	2	8	4	2

*Despite lack of 1:1 numerical correspondence in scores across subjects sexual domain strata in EPIC-CP model are numerically similar to those previously used in EPIC-26 model, ie 0 vs 100, 2 vs 83 and 4 vs 67 (fig. 1).

†Log odds of functional erection after radical prostatectomy = 1.46 – 0.35 pretreatment EPIC-CP sexual score – 0.59 (age per 10 years) + 1.31 (nerve sparing) + 0.86 (PSA 10 ng/dl or less).



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How does EPIC-CP perform in the real-world?

- Is it **FEASIBLE** to use outside of research? Is there a **discrepancy** between patient-reported and physician-reported outcomes?
- 482 Robotic Prostatectomy patients at BIDMC from 2010 to 2014
- EPIC-CP Questionnaires used in routine practice to assess QOL
 - No research personnel involved in administration
 - Given at baseline and at every follow-up visit after surgery
 - Prospective administration (Point of care in clinic)
- Reviewed demographic and QOL results
- 708 EPIC-CP questionnaires reviewed at time of submission



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EPIC-CP can be downloaded at
<http://www.bidmc.org/epic>

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Clinical Use of Expanded Prostate Cancer Index Composite for Clinical Practice to Assess Patient Reported Prostate Cancer Quality of Life Following Robot-Assisted Radical Prostatectomy

Andrew A. Wagner,* Philip J. Cheng,* Arie Carneiro, Ostap Dovirak, Arjun Khosla, Kimberly N. Taylor, Catrina M. Crociani, Kyle C. McNally, Andrew Percy, Lauren E. Dewey, Martin G. Sanda and Peter Chang†

Table 1. Characteristics of 482 patients

% Age greater than 60	48.9
% Race:	
White	76.7
Black	11.5
Other	11.1
Not reported	1.7
Mean ± SD body mass index (kg/m ²)	27.8 ± 4.25
Mean ± SD Charlson comorbidity index	4.73 ± 1.1
Mean ± SD prostate size (ml):	
Transrectal ultrasound	40.8 ± 20
Digital rectal examination	36.7 ± 11.5
Prostate specific antigen (ng/ml):	
Mean ± SD	6.3 ± 5.1
% Less than 4	26.1
% 4–10	63.4
% Greater than 10	10.5
% Gleason score on biopsy:	
Less than 7	40.9
7	50.0
Greater than 7	5.1
% Clinical stage:	
T1	62.6
T2	27.2
T3	6.2
Unknown	10.0
% Nerve sparing*	19.7

*Wide resection of neurovascular bundles bilaterally

Table 2. Patient reported HRQOL scores using EPIC-CP

	Baseline	3 Mos	6 Mos	12 Mos
Urinary incontinence	0.6 ± 0.2	3.1 ± 2.3*	2.2 ± 2.1*	1.6 ± 1.7
Urinary irritation/obstruction	1.9 ± 2.4	1.6 ± 1.7	1.1 ± 1.5	1.1 ± 1.5†
Bowel symptoms	0.6 ± 1.4	0.8 ± 1.8†	0.6 ± 1.5	0.4 ± 1.3
Sexual dysfunction	2.4 ± 2.8	7.0 ± 3.5*	5.7 ± 3.1*	5.9 ± 3.3*
Hormonal symptoms	1.2 ± 1.8	1.3 ± 1.8	1.1 ± 1.7	1.5 ± 1.7
Overall prostate Ca life quality	6.6 ± 1.8	13.3 ± 6.6†	10.5 ± 6.5†	10.2 ± 5.9†

*HRQOL difference statistically and clinically significant vs pretreatment baseline.

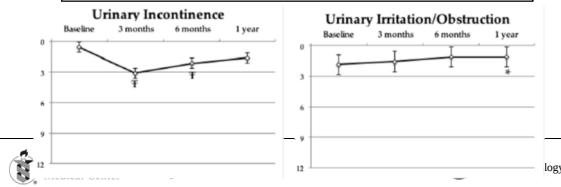
†HRQOL difference statistically significant vs pretreatment baseline (p < 0.05).

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Urinary outcomes

- No significant discrepancy between physician- and patient-reported

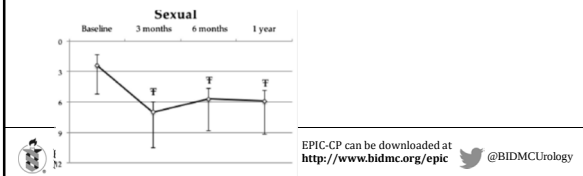
	Physician-reported Pad-free rate	Patient-reported Pad-free rate using EPIC-CP
Pre-treatment	99%	99%
3 months	48%*	39%
6 months	63%	70%
1 year	76%	76%



Sexual outcomes

- Physicians **overestimated** rates of sexual function return

	Physician-reported Functional Erection rate	Patient-reported Functional Erection rate using EPIC-CP
Pre-treatment	82%*	72%
3 months	18%	12%
6 months	38%*	28%
1 year	45%*	23%



EPIC-CP can be downloaded at
<http://www.bidmc.org/epic> @BIDMCUrology

SO WHAT? Why use PROs or EPIC-CP in my practice?

- Benefits to **patient**:
 - Accurate and objective information
 - Gives patient a voice to convey their problems
 - Can influence treatment decision making
- Benefits to **practitioner**:
 - Snapshot of QOL before even entering the room
 - Identify problems to discuss, ?additional consultations
 - May make visit **more efficient**
 - Fulfills components of ROS
 - Mandated PRO use in the policy pipeline

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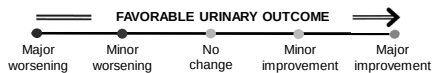
Predicting Post-Treatment Urinary Outcomes

Chang et al Feb 2017

	Worsened	Improved
All subjects (1021)	28%	23%
Radical prostatectomy (522)	27%	28%
External radiotherapy (239)	24%	25%
Brachytherapy (260)	37%	12%

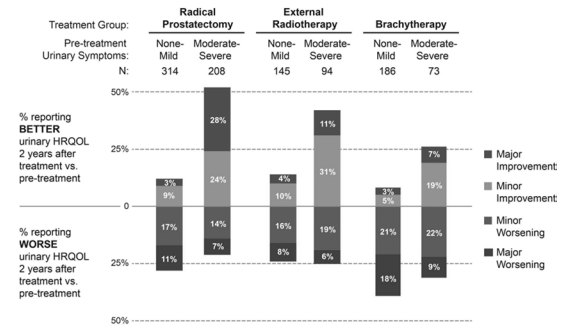
- Who gets better and who gets worse?

- Categorized overall urinary bother change into an ordinal scale from major worsening to major improvement



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Mod-Severe AUA-SI score predicts treatment-induced urinary symptom relief, especially for radical prostatectomy



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Regulations and Recommendations

- International Consortium for Health Outcomes Measurement (ICHOM) included EPIC-26 as a component of its standard set for localized prostate cancer
- American Cancer Society Survivorship Guidelines
 - "Annually assess for the presence of long-term or late effects of prostate cancer and its treatment using EPIC-CP"
- Payor regulations

Beth Israel Deaconess Medical Center HARVARD MEDICAL SCHOOL TEACHING HOSPITAL Noonan EM et al. Primary Care of the Prostate Cancer Survivor. Am Fam Physician. 2016 May 1;93(9):764-771 @BIDMCUrology



Advances in Systemic Therapy for Muscle Invasive Bladder Cancer

Comprehensive Review of Urology series

Richard J. Lee, M.D., Ph.D.

Assistant Professor of Medicine, Harvard Medical School
Assistant Physician, Mass General Cancer Center
31 August 2018



Relevant disclosures

None



Objectives

Bladder cancer

- To understand the role of peri-operative chemo
- To understand the regimens in common use
- To consider future targets for therapy



Bladder cancer: Scope of the problem

US estimates for 2018: 81,190 new cases, 17,240 deaths

Estimated New Cases

Cancer Site	Estimated New Cases	%
Prostate	164,690	19%
Lung & bronchus	121,680	14%
Colon & rectum	75,610	9%
Urinary bladder	62,380	7%
Melanoma of the skin	55,150	6%
Kidney & renal pelvis	42,680	5%
Non-Hodgkin lymphoma	41,730	5%
Oral cavity & pharynx	37,160	4%
Leukemia	35,030	4%
Liver & intrahepatic bile duct	30,610	4%
All Sites	856,370	100%

Estimated Deaths

Cancer Site	Estimated Deaths	%
Lung & bronchus	83,550	26%
Prostate	29,430	9%
Colon & rectum	27,390	8%
Pancreas	23,020	7%
Liver & intrahepatic bile duct	20,540	6%
Leukemia	14,270	4%
Esophagus	12,850	4%
Urinary bladder	12,520	4%
Non-Hodgkin lymphoma	11,510	4%
Kidney & renal pelvis	10,910	3%
All Sites	323,630	100%

Global numbers in 2012:

- 429,800 new cases (9th most common)
- 165,100 deaths (13th leading cause of cancer death)



Bladder Cancer: Overview

Pros/cons of neoadjuvant and adjuvant chemotherapy

Current standard chemotherapy regimens

Evidence for adjuvant chemotherapy

Evidence for neoadjuvant chemotherapy

A look into the future

The #1 goal of peri-operative chemotherapy:
Improve cure rates.



Neoadjuvant or Adjuvant Chemo?

Neoadjuvant → Surgery → Adjuvant

	Neoadjuvant	Advantage	Adjuvant
Decision making	Clinical staging	➡	Pathologic staging (directed delivery)
Ability to affect micrometastatic disease	Pre-op, when tumor burden is low	➡	Months after diagnosis; post-op complications may delay therapy
Evidence of survival benefit	Phase 3 RCTs	➡	No adequately powered trials



Understanding the Risk: Standard Chemotherapy for Bladder Cancer

MVAC
Methotrexate
Vinblastine
Doxorubicin
Cisplatin

GC
Gemcitabine
Cisplatin

General risks
Neutropenia
Anemia
Thrombocytopenia
Nausea/vomiting
Mouth sores
Hair loss
Renal dysfunction
Neuropathy
Tinnitus
Death

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Standard Chemotherapy for Bladder Cancer

MVAC: 28 day cycle
Methotrexate: 30mg/m² d1,15,22
Vinblastine: 3mg/m² d2, 15,22
Doxorubicin: 30mg/m² d2
Cisplatin: 70mg/m² d2

ddMVAC: 14 day cycle
Methotrexate: 30mg/m² d1
Vinblastine: 3mg/m² d2
Doxorubicin: 30mg/m² d2
Cisplatin: 70mg/m² d2

GC: 21 day cycle
Gemcitabine: 1000mg/m² d1,8
Cisplatin: 70mg/m² d1

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MVAC vs. GC: which is better? Evidence from the metastatic setting

Patients:
Locally advanced
And Metastatic
Bladder Cancer

→

Randomize

MVAC (n=202)

GC (n=203)

Primary endpoint: overall survival (OS)

Secondary endpoints: objective tumor response, duration of response, time to progression, toxicity

von der Maase et al. J Clin Oncol 2000; 18: 3068-3077.
Roberts et al. Annals Oncol 2006; 17: v118-v122.

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MVAC vs. GC: which is better?

	MVAC	GC
Grade 3 or 4 neutropenia	82%	71%
Neutropenic fever	14%	2%
Neutropenic sepsis	12%	1%
Grade 3 or 4 mucositis	22%	1%
Treatment related mortality	3%	1%

von der Maase et al. J Clin Oncol 2000; 18: 3068-3077.

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Metastatic bladder cancer: dismal survival

No FDA-approved second-line therapies until 2016!

Roberts et al. Annals Oncol 2006; 17: v118-v122.

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MVAC vs. GC: which is better?

In metastatic disease, GC has become the standard due to:

- similar response rate
- similar progression free-survival
- similar overall survival
- better toxicity profile

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Overview

Pros/cons of neoadjuvant and adjuvant chemotherapy
Current standard chemotherapy regimens
Evidence for adjuvant chemotherapy
Evidence for neoadjuvant chemotherapy
A look into the future



13

Adjuvant chemotherapy: retrospective studies

798 patients with RC between 1993-2011
 Extravesical and/or node (+) offered adjuvant cisplatin-based chemo
 23% received adjuvant chemo

Category	HR	95% CI	p
End point: Overall mortality			
Age (continuous variable, per-year increase)	1.02	1.01-1.04	0.0001
Charlson score (continuous variable, per-unit increase)	1.12	1.06-1.18	<0.0001
ASA classes 3-4 (vs 1-2)	1.64	1.32-2.04	<0.0001
Extravesical disease (vs bladder confined disease)	2.11	1.69-2.62	<0.0001
Positive lymph nodes (vs negative lymph nodes)	2.24	1.64-2.62	<0.0001
Lymph node density (continuous variable, per-10% increase)	1.14	1.07-1.21	<0.0001
Any neoadjuvant chemotherapy (vs none)	1.87	1.28-2.75	0.0014
Adjuvant cisplatin-based chemotherapy (vs none)	0.50	0.38-0.66	<0.0001
End point: Bladder cancer-specific mortality			
Extravesical disease (vs bladder confined disease)	2.10	1.58-2.79	<0.0001
Positive lymph nodes (vs negative lymph nodes)	3.83	2.81-5.22	<0.0001
Any neoadjuvant chemotherapy (vs none)	2.47	1.54-3.97	0.0002
Adjuvant cisplatin-based chemotherapy (vs none)	0.71	0.52-0.97	0.0321

Froehner et al. *Eur Urol* 2016; **69**: 984-987.

Adjuvant chemotherapy for bladder cancer:
Reported RCTs

Institution	N	Regimen	Survival benefit	Completed accrual
USC	91	Cis/dox	Yes	Yes
U of Mainz, Germany	49	MVAC/MVEC	Yes	Yes
Swiss Gp for Clin Can Res	77	Cisplatin	No	Yes
Stanford	55	CMV	No	Yes
US Intergroup	114	MVAC	No	No
Italian multicenter	194	GC	No	No
SOGUG (Spain)	142	PCG	Yes	No

Skinner et al. *J Urol* 1991; **145**: 459-464.

Stockle et al. *J Urol* 1995; **153**: 47-52.

Studer et al. *J Urol* 1994; **152**: 83-84.

Freiha et al. *J Urol* 1996; **155**: 495-499.

Stadler et al. *J Clin Oncol* 2011; **29**: 3443-3449.

Cognigni et al. *Ann Oncol* 2012; **23**: 695-700.

Paz-Ares et al. *J Clin Oncol* 2010; **28** (Suppl): 18s.



15

Adjuvant chemotherapy: meta-analysis

Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

Jeffrey J. Leow^{a,b,c}, William Martin-Doyle^a, Padma S. Rajagopal^a, Chirayu G. Patel^a, Erin M. Anderson^a, Andrew T. Rothman^a, Richard J. Cole^d, Yuksel Uzun^e, Steven L. Chang^f, Toni K. Choueiri^g, Joaquim Bellmunt^{h,i,j}

^aHarvard School of Public Health, Harvard University, Boston, MA, USA; ^bCenter for Surgery and Public Health, Brigham and Women's Hospital, Boston, MA, USA; ^cDivision of Urology, Brigham and Women's Hospital, Boston, MA, USA; ^dDepartment of Pathology, University of Miami Miller School of Medicine, Miami, FL, USA; ^eBladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA, USA; ^fUniversity Hospital del Mar (IMM), Barcelona, Spain

Update from 2005

945 patients in 9 RCTs

Findings:

OS: HR 0.77 (0.59-0.99; $p = 0.049$)

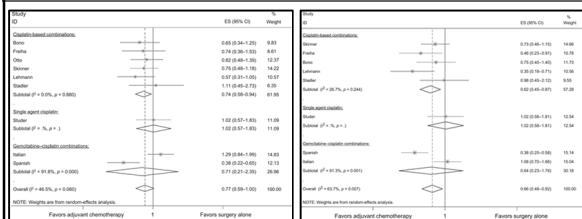
DFS: HR 0.66 (0.45-0.91; $p = 0.014$)

DFS benefit seen in patients with (+) nodes

Leow et al. *Eur Urol* 2014; **66**: 42-54.



Adjuvant chemotherapy: meta-analysis



OS

PFS

Leow et al. *Eur Urol* 2014; **66**: 42-54.

What about timing of chemo?
Immediate vs deferred

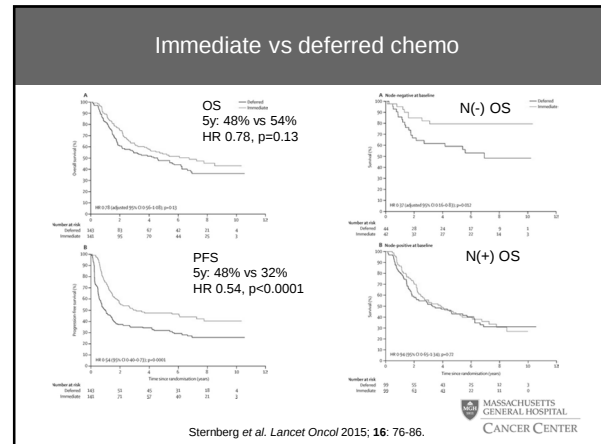
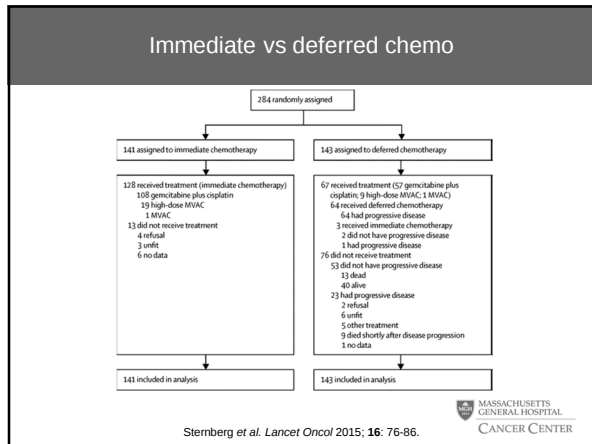
Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial

Cara N Sternberg, Joanna Skoneczna, J Martin Kest, Peter Albers, Sophie D Fouca, Mads Agerholm, Helinde Dumaz, Maria de Santis, Christine Thibodeau, Michael G Leahy, John D Chester, Antony Verheij, Gerdie Deugnot, Lutz Wood, J Alfred Wille, Ronald de Wit, Lionel Goffin, Luc Sengler, George Thalmann, Danielle Chaperon, Frédéric Rolland, Laurent Mignot, Sørensen Sander, Paul Sprondel, John Graham, Florence Joly, Sandrine Marrou, Laurence Collette, Richard Sylvester, for the European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group, Groupe d'Etude des Tumeurs Urologiques, National Cancer Research Institute Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, and German Association of Urologic Oncology (AUGO)

- Phase III intergroup trial (Europe, Canada)
- pT3-T4 or pN1-N3 and M0 disease
- Immediate versus deferred chemotherapy at time of relapse
- Chemo: cis/gem or MVAC
- 284 of planned 660 pts accrued (2002 – 2008)

Sternberg et al. *Lancet Oncol* 2015; **16**: 76-86.





Adjuvant chemotherapy for bladder cancer

No definitive prospective data support adjuvant chemotherapy

- underpowered studies
- failure to complete accrual
- meta-analyses: suggestive of benefit

Do we give it?

In practice, adjuvant chemo is often given to patients with node-positive and/or extra-vesical disease who can tolerate chemo

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Overview

Pros/cons of neoadjuvant and adjuvant chemotherapy

Current standard chemotherapy regimens

Evidence for adjuvant chemotherapy

Evidence for neoadjuvant chemotherapy

A look into the future

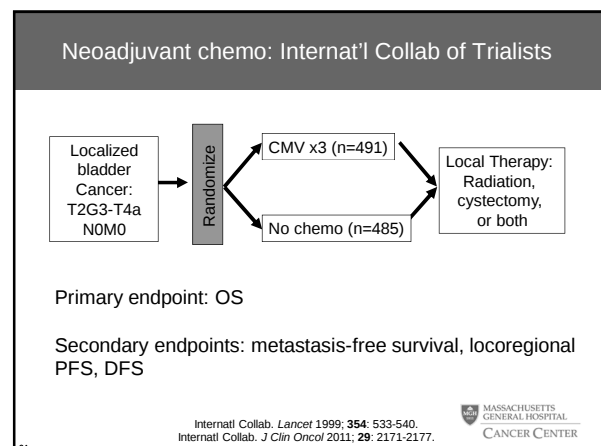
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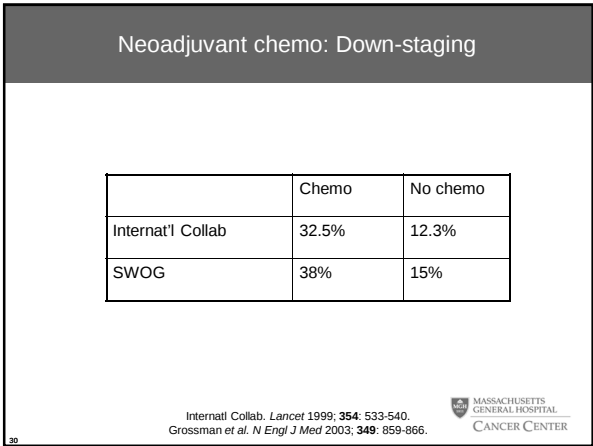
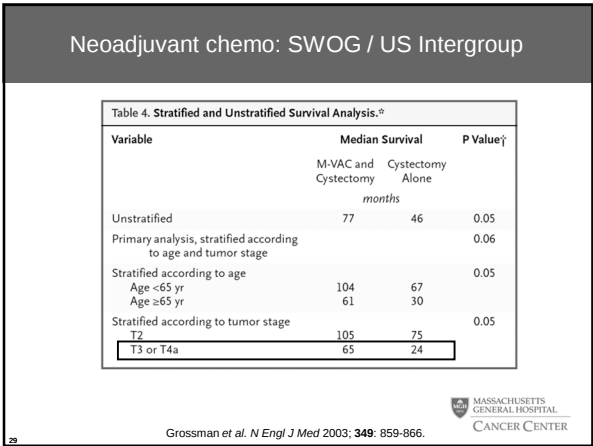
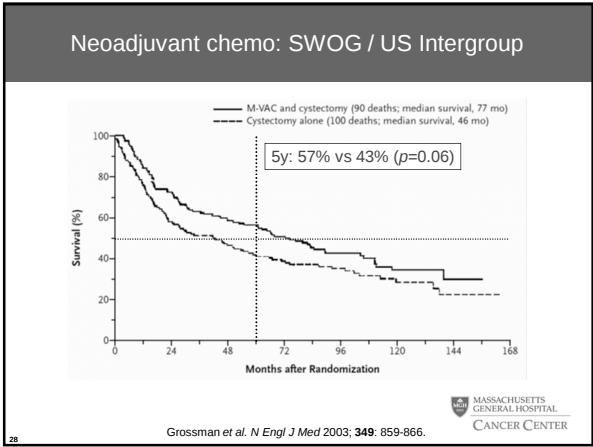
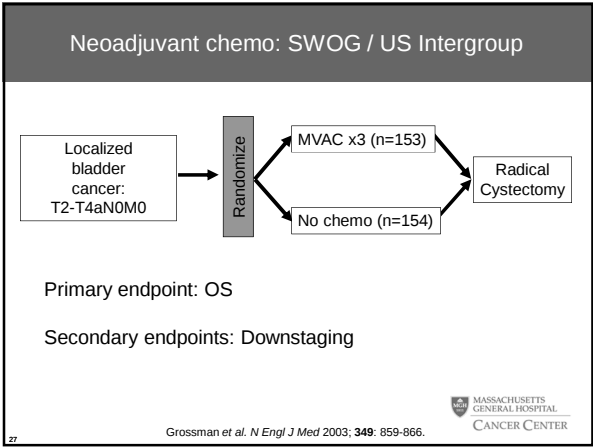
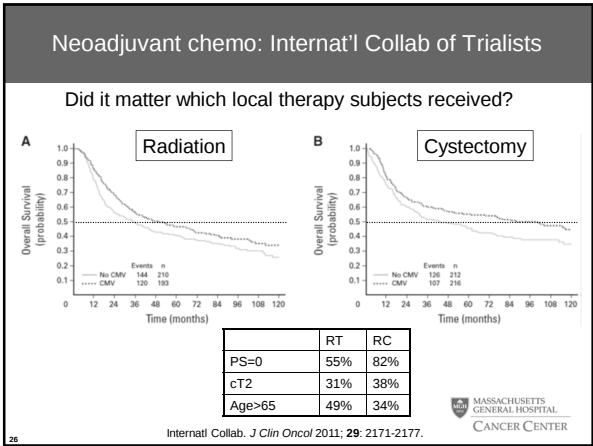
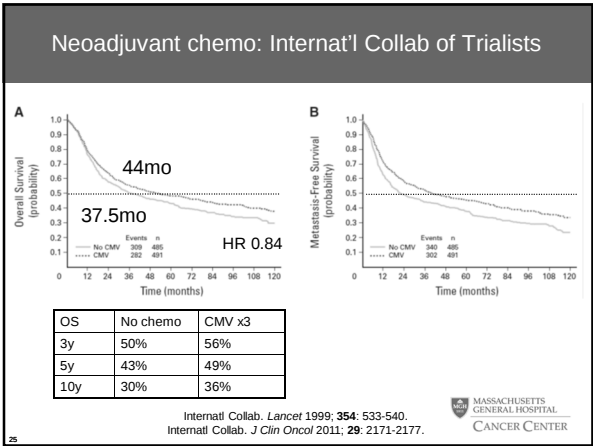
Neoadjuvant Chemo: Randomized Trials

Trial	N	Eligibility	Regimen	Survival Benefit	Comment
Nordic Cystectomy I	325	T1G3-T4a NxM0	(Cisplatin + doxorubicin) x2	No	Nonconventional chemo regimen + neoadjuvant RT
Nordic Cystectomy II	317	T2-T4a NxM0	(Cisplatin + methotrexate) x3	No	Nonconventional chemo regimen
Internat'l Collab of Trialists	976	T2G3-T4a NOM0	CMV x3	Yes	Local therapy: RT, RC, RT+RC
SWOG/ US Intergroup	317	T2-T4 NOM0	MVAC x3	Yes	

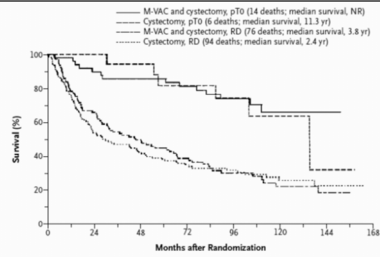
RT=radiation therapy; RC=radical cystectomy

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Neoadjuvant chemo: SWOG / US Intergroup



No. at Risk	0	24	48	72	96	120	144	168
M-VAC and cystectomy, pT0	48	43	40	37	26	12	2	
Cystectomy, pT0	18	17	15	12	10	4	1	
M-VAC and cystectomy, RD	105	69	52	38	20	11	4	
Cystectomy, RD	136	71	52	37	27	14	6	

Grossman et al. *N Engl J Med* 2003; **349**: 859-866.MASSACHUSETTS
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31

Neoadjuvant or Adjuvant Chemo

Neoadjuvant → Surgery → Adjuvant

	Neoadjuvant	Advantage	Adjuvant
Decision making	Clinical staging	➔	Pathologic staging (directed delivery)
Ability to affect micrometastatic disease	Pre-op, when tumor burden is low	➔	Months after diagnosis; post-op complications may delay therapy
Evidence of survival benefit	Phase 3 RCTs	➔	No adequately powered trials

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32

Other neoadjuvant chemotherapy regimens?

Inst	Regimen	N	Eligibility	Path CR	Comment
Brazil	GC x3	19	T2-4N0-1M0	27%	50% T2
MSKCC	GC x4	42	T2-4aN0M0	26%	45% T2
Japan	GC x2	22	T2-4N0-1M0	50%	68% T2
Cleveland Clinic	GC	20	T2-4aN0-2M0	10%	79% T2, 14% N+
Rochester	GC	25	T2-4NanyM0	20%	
UK	AMVAC x3-4	80	T2-4aN0-2M0	43%	15% N+
MGH	GC	29	T2-4N0M0	48%	48% T2
Multi	ddMVAC	100	T3-4aN0M0	28%	
	GC	219		15%	

Herchenhorn et al. *Int Braz J Urol* 2007; **33**: 630-638.
 Dash et al. *Cancer* 2008; **113**: 2471-2477.
 Kaneko et al. *Jpn J Clin Oncol* 2011; **41**: 908-914.
 Weight et al. *Cancer* 2009; **115**: 792-799.

Scosyrev et al. *Cancer* 2012; **118**: 72-81.
 Blick et al. *Cancer* 2012; **118**: 3920-3927.
 Zargar et al. *J Urol* 2018; **199**: 1452-1458.

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Bladder Cancer: Conclusions/Review

Pros/cons of neoadjuvant and adjuvant chemotherapy

Current standard chemotherapy regimens

➔ GC, MVAC

Evidence for adjuvant chemotherapy

➔ no large prospective studies show a benefit

Evidence for neoadjuvant chemotherapy

➔ MVAC x3, CMV x3

➔ potential for other regimens with higher path CR

A look into the future

➔ bladder cancer needs more attention!

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Targeted therapies?

The first cloned human oncogene (RAS, 1982) was from a bladder cancer cell line....

Mutated genes as potential targets:

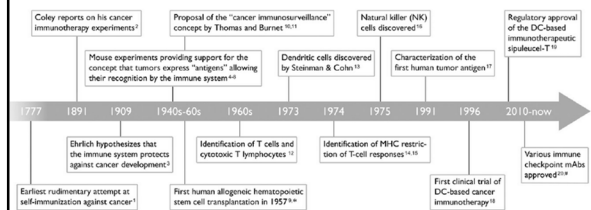
- FGFR3
- RAS (HRAS, KRAS, NRAS)
- PIK3CA

What about immunotherapy?

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History of immuno-oncology

Anguille et al. *Pharmacol Rev* 2015; **67**: 731-753.MASSACHUSETTS
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[illegible]Chen et al. *Clin Cancer Res* 2012; **18**: 6580-6587

Figure 1: Somatic mutation frequency (MF) in 128 cancer types. The plot shows MF on a log scale (0.001 to 1000) for 128 cancer types. A color scale on the left indicates the number of samples (n) for each cancer type, ranging from 1 to 22. A box highlights the top 10 cancer types with the highest MF: Kidney renal clear cell, Kidney papillary cell, Ovarian, Glioma, Glioblastoma multiforme, Cervical, OLSL, Head and neck, Colorectal adenoma, and Adenocarcinoma. A legend at the bottom identifies the cancer types by color: Bladder, Breast, Colon, Esophagus, Liver, Lung, Pancreas, Prostate, Skin, Stomach, Testis, Uterus, and Vagina.

Lawrence et al. *Nature* 2013; **499**: 214-218.

Diagram illustrating the process of dendritic cell maturation and its role in cancer immunotherapy. The process starts with a BCG (Bacillus Calmette-Guérin) infection, leading to the processing of dendritic cells. These cells then undergo dendritic maturation, which involves the presentation of antigens to T cells. The diagram shows the progression from a dendritic cell to a mature dendritic cell, which then interacts with a T cell. The mature dendritic cell is shown with various markers: MHC II, CD80, CD86, CD11c, CD11b, CD11a, CD11d, CD11e, CD11f, CD11g, CD11h, CD11i, CD11j, CD11k, CD11l, CD11m, CD11n, CD11o, CD11p, CD11q, CD11r, CD11s, CD11t, CD11u, CD11v, CD11w, CD11x, CD11y, CD11z, CD11aa, CD11ab, CD11ac, CD11ad, CD11ae, CD11af, CD11ag, CD11ah, CD11ai, CD11aj, CD11ak, CD11al, CD11am, CD11an, CD11ao, CD11ap, CD11aq, CD11ar, CD11as, CD11at, CD11au, CD11av, CD11aw, CD11ax, CD11ay, CD11az, CD11ba, CD11bb, CD11bc, CD11bd, CD11be, CD11bf, CD11bg, CD11bh, CD11bi, CD1

Figure 1 | Tentative model of the mechanism of action of BCG in bladder cancer.

Redelman-Sidi et al. *Nat Rev Urol* 2014; **11**: 153-162.

LETTER

MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Safety and activity of pembrolizumab in patients with local advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study

Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Avelumab, an Anti-Programmed Death-Ligand 1 Antibody, in Patients With Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase Ib Study

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Safety and Efficacy of Durvalumab (MEDI4736), an Anti-Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer

Powles et al. *Nature* 2014; **515**: 558-562.
Massard et al. *J Clin Oncol* 2016; **34**: 3119-3125
Plimack et al. *Lancet Oncol* 2017; **18**: 212-220.
Sharma et al. *Lancet Oncol* 2017; **18**: 312-322.
Apolo et al. *J Clin Oncol* 2017; **35**: 2117-2124.

	Atezo	Avelu	Durva	Nivo	Pembro
Target	PD-L1	PD-L1	PD-L1	PD-1	PD-1
N	67	44	191	265	33 PD-L1+
ORR	25%	18.2%	17.8%	19.6%	26%
mOS	NR	13.7 mo	18.2 mo	8.7 mo	13 mo
PD-L1 test	Ventana SP142	DAKO 73- 10	Ventana SP263	DAKO 28-8	DAKO 22C3
mOS high expressors	NR	NR vs 12.9 mo	20.0 mo vs 8.1 mo	11.3 mo	n/a
G3-4 AEs	4.4%	6.8%	6.8%	18%	15%

Powles *et al.* *Nature* 2014; **515**: 558-562.
Massard *et al.* *J Clin Oncol* 2016; **34**: 3119-3125
Plimack *et al.* *Lancet Oncol* 2017; **18**: 212-220.
Sharma *et al.* *Lancet Oncol* 2017; **18**: 312-322.
Apolo *et al.* *J Clin Oncol* 2017; **35**: 2117-2124.

Ph 1 atezolizumab (MPDL3280A) for bladder cancer

Adults (>18 yo)

Incurable metastatic solid tumor or hematologic malignancy

ECOG PS 0-1

Tissue available for PD-L1 assessment

Initially open only to PD-L1 IHC 2/3 patients, but eventually expanded

Atezolizumab 15 mg/kg mg IV d1 of 21-d cycles until PD or unacceptable toxicity

n = 67

Primary Endpoints:

Safety, adverse events

Additional Endpoints (N=67 evaluable for efficacy):

Overall response by RECIST v1.1

Response by PD-L1 status

Cytokine (IL-18, IFN-g) levels by luminex

CD3, CD8, HLA-DR, Ki67 by FACS

IHC grade 0 if <1%, 1 if 1-5%, 2 if 5-10%, 3 if ≥10% in tumor, macrophages, DCs, lymphocytes (total percentage over the 4 categories).

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Powles et al. Nature 2014; 515: 558-562.

Efficacy of atezolizumab

Tumour-infiltrating immune cells and objective response rates

	Objective response rate n (%)	Stable disease n (%)	Progressive disease n (%)
IHC 2/3 (n = 30)	13 (43.3) (95% CI: 25.5-62.6)	8 (26.7)	8 (26.7)
IHC 3 (n = 10)	5 (50.0) (95% CI: 22.2-77.8)	2 (20.0)	3 (30.0)
IHC 2 (n = 20)	8 (40.0) (95% CI: 20.9-63.9)	6 (30.0)	5 (25.0)
IHC 0/1 (n = 35)	4 (11.4) (95% CI: 4.0-26.3)	13 (37.1)	13 (37.1)
IHC 1 (n = 23)	3 (13.0) (95% CI: 3.7-31.7)	8 (34.8)	8 (34.8)
IHC 0 (n = 12)	1 (8.3) (95% CI: 0.4-34.9)	5 (41.7)	5 (41.7)

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Powles et al. Nature 2014; 515: 558-562.

Efficacy of atezolizumab

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Powles et al. Nature 2014; 515: 558-562.

Atezolizumab: safety

Table 2 | Treatment-related adverse events occurring in two or more patients (grade 1-2) or in one patient (grade 3-4)

Treatment-related adverse events* (n = 68)	All grades (n (%))	Grade 3-4 (n (%))
All	39 (57.4)	3 (4.4)
Decreased appetite	8 (11.8)	0
Fatigue	8 (11.8)	0
Nausea	8 (11.8)	0
Pyrexia	6 (8.8)	0
Asthenia	5 (7.4)	1 (1.5)
Chills	3 (4.4)	0
Influenza-like illness	3 (4.4)	0
Lethargy	3 (4.4)	0
Anaemia	2 (2.9)	0
Arthralgia	2 (2.9)	0
Bone pain	2 (2.9)	0
Hyperthermia	2 (2.9)	0
Pain	2 (2.9)	0
Platelet count decrease	2 (2.9)	0
Pruritus	2 (2.9)	0
Thrombocytopenia	2 (2.9)	1 (1.5)
Vomiting	2 (2.9)	0
Blood phosphorus decrease	1 (1.5)	1 (1.5)

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Powles et al. Nature 2014; 515: 558-562.

IMvigor 210:
Ph 2 atezolizumab for bladder cancer

Adults (>18 yo)

Locally Advanced or mUC

Progression on or following platinum-based chemotherapy

ECOG PS 0-1

Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis

N = 316

Atezolizumab 1,200 mg IV d1 of 21 day cycles until PD or unacceptable toxicity

Primary Endpoints:

ORR by RECIST v1.1

Modified RECIST per investigator

Additional Endpoints:

Duration of response

Response by PD-L1 status

PFS

OS

Incidence of adverse events

Incidence of antibodies to atezolizumab

Maximum serum concentration of atezolizumab

Another cohort (not shown) examined effects of Atezolizumab in untreated platinum ineligible patients

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Rosenberg et al. Lancet 2016; 387: 1909-1920.

IMvigor 210:
Efficacy of atezolizumab

	Patients, n	Objective response rate, n (%) [95% CI]	Complete response	Partial response	Stable disease	Progressive disease
RECIST version 1.1 criteria by independent review						
IC2/3	100	26 (26% [18-36])	11 (11%)	15 (15%)	16 (16%)	44 (44%)
IC1/2/3	207	37 (18% [13-24])	13 (6%)	24 (12%)	34 (16%)	107 (52%)
All patients	310	45 (15% [11-19])	15 (5%)	30 (10%)	59 (19%)	159 (51%)
IC1*	107	11 (10% [5-18])	2 (2%)	9 (8%)	18 (17%)	63 (59%)
IC0*	103	8 (8% [3-15])	2 (2%)	6 (6%)	25 (24%)	52 (50%)
Modified RECIST criteria by investigator review						
IC2/3	100	27 (27% [19-37])	8 (8%)	19 (19%)	31 (31%)	28 (28%)
IC1/2/3	207	45 (22% [16-28])	14 (7%)	31 (15%)	58 (28%)	74 (36%)
All patients	310	58 (19% [15-24])	16 (5%)	42 (14%)	92 (30%)	110 (35%)
IC1*	107	18 (17% [10-25])	6 (6%)	12 (11%)	27 (25%)	46 (43%)
IC0*	103	13 (13% [7-21])	2 (2%)	11 (11%)	34 (33%)	36 (35%)

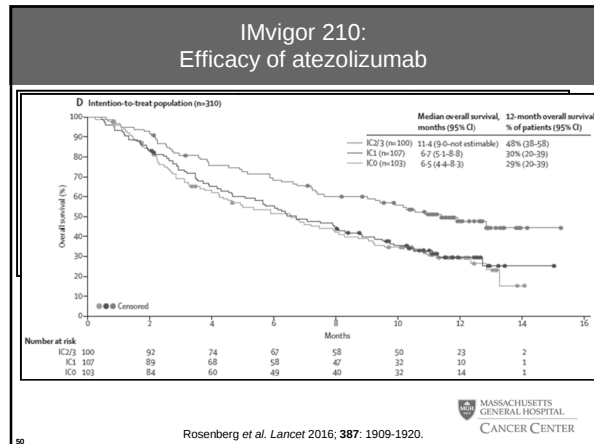
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Rosenberg et al. Lancet 2016; 387: 1909-1920.

741



Patient characteristics

IMvigor 210	Ph1 Trial
• Median Age 66	• Median Age 65
• 35% with CrCl <60 mL/min	• 33.3% with CrCl <60 mL/min
• 40% with ≥2 prior regimens	• 71.6% with ≥2 prior regimens
• 78% with visceral metastasis	• 50% with visceral metastasis
• 62% ECOG PS1	• 59.1% ECOG PS1
• 22% Hb <10 g/dL	• 18.5% Hb <10 g/dL
• 31% with liver metastasis	• 22% with liver metastasis

Rosenberg et al. *Lancet* 2016; **387**: 1909-1920.

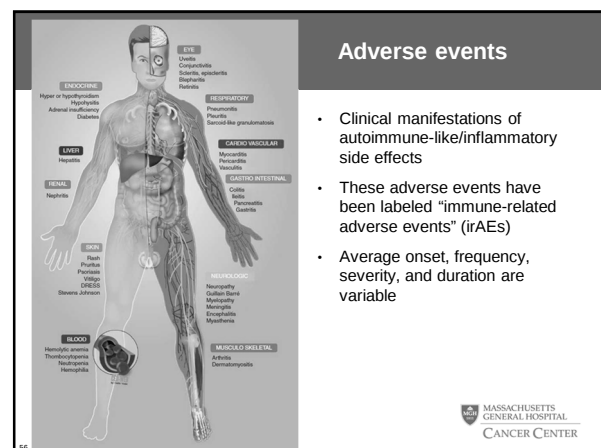
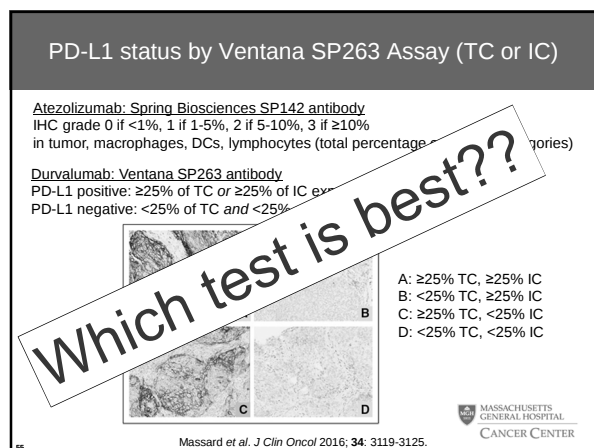
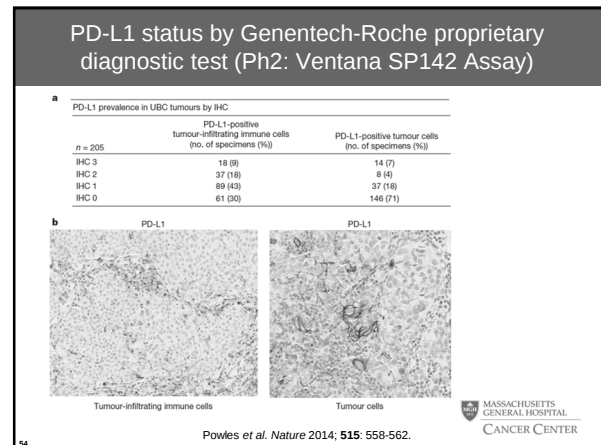
IMvigor 210: AEs and atezolizumab

Any adverse event	Any grade	Grade 3-4
Fatigue	215 (59%)	50 (16%)
Nausea	93 (30%)	5 (2%)
Decreased appetite	42 (14%)	0
Pruritis	36 (12%)	2 (1%)
Pyrexia	31 (10%)	1 (<1%)
Diarrhoea	28 (9%)	1 (<1%)
Rash	24 (8%)	1 (<1%)
Arthralgia	23 (7%)	1 (<1%)
Vomiting	21 (7%)	2 (1%)
Dyspnoea	18 (6%)	1 (<1%)
Anaemia	10 (3%)	2 (1%)
Aspartate aminotransferase increased	9 (3%)	3 (1%)
Pneumonitis	10 (3%)	2 (1%)
Hypotension	7 (2%)	2 (1%)
Hypertension	5 (2%)	2 (1%)
Colitis	3 (1%)	3 (1%)
Colitis	3 (1%)	2 (1%)

Adverse events reported up until data cutoff on Sept 14, 2015.

Table 3: Treatment-related adverse events in the 310 patients who received atezolizumab

Rosenberg et al. *Lancet* 2016; **387**: 1909-1920.



Ph 3 pembrolizumab: KEYNOTE-045

A Overall Survival

Hazard ratio for death, 0.73 (95% CI, 0.59-0.91)
P=0.002

Patients Who Survived (%)

Months

Pembrolizumab
Chemotherapy

No. at Risk	270	226	194	169	147	131	87	54	27	13	4	0	0
Pembrolizumab	270	226	194	169	147 <td>131</td> <td>87</td> <td>54</td> <td>27</td> <td>13</td> <td>4</td> <td>0</td> <td>0</td>	131	87	54	27	13	4	0	0
Chemotherapy	272	232	177	138	109	89	55	27	14	3	0	0	0

B Progression-Free Survival

Hazard ratio for disease progression or death, 0.58 (95% CI, 0.43-1.19)
P=0.02

Patients without Disease Progression or Death (%)

Months

Pembrolizumab
Chemotherapy

No. at Risk	270	165	85	73	56	51	23	16	7	0	0
Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0
Chemotherapy	272	188	85	56	27	17	10	5	1	0	0

The key detail is the tail

Ph 3 pembrolizumab: Time of response happens early and can be sustained

Legend:
 - First radiologic assessment of response
 - Ongoing study treatment
 - Disease progression or death

Patients with a Response to Pembrolizumab (N=57)

Patients with a Response to Chemo (N=11)

Months

60
50
40
30
20
10
0

0 3 6 9 12 15 18

Belmont et al. *N Engl J Med* 2017; **376**: 1015-1026.

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Cisplatin-ineligible patients

KEYNOTE-052
Pembrolizumab
N=370
ORR: 24% (89/370)
PD-L1 $\geq 10\%$: ORR 38% (42/110)

IMvigor 210
Atezolizumab
N=119
ORR: 23% (range: 21%-28% from IC0-IC2/3)
Med OS 15.9 mos
TMB, TCGA subtype associated with response

Balar *et al. Lancet Oncol* 2017; **18**: 1483-1492.
Balar *et al. Lancet* 2017; **389**: 67-76.

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So what's next?

Bladder cancer challenges and needs

How do we best select patients?

- is there a "best test" for PD-L1 status?
- is there a "best time" to check PD-L1 status?

High tolerability but high cost and low-ish response rates: can we afford to treat everyone?

Where else might immune checkpoint therapy fit in the bladder cancer treatment continuum?



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Immune checkpoint clinical trials that are underway or proposed in the bladder cancer continuum

<u>NMIBC</u> High-grade BCG-refractory	<u>MIBC</u> Neoadjuvant Adjuvant	<u>Metastatic</u> 1L cis-ineligible 1L cis-eligible Maintenance 2L post-platinum
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63

Bladder Cancer: Conclusions/Review

Pros/cons of neoadjuvant and adjuvant chemotherapy

Current standard chemotherapy regimens

Evidence for adjuvant chemotherapy

Evidence for neoadjuvant chemotherapy

A look into the future

→ a future for IO therapy in the bladder cancer continuum of care


64

Antenatal Hydronephrosis: Diagnosis and Management



Children's Hospital Colorado

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Learning Objectives

- To review the classification of antenatal and postnatal imaging
- To review diagnoses associated with antenatal hydronephrosis
- To discuss management options and outcomes

Antenatal Hydronephrosis

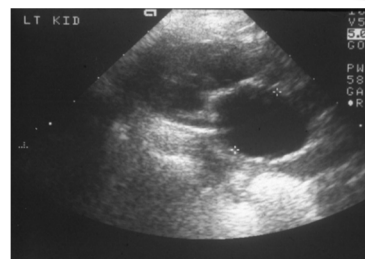
- Common abnormality on antenatal ultrasound
 - 1-5% of pregnancies
- Wide spectrum of conditions
 - Transient hydronephrosis
 - Vesicoureteral reflux
 - Upper tract/lower tract obstruction
 - Renal dysgenesis
- Goal of early diagnosis and treatment is **renal preservation**

AP Diameter

- Most studied measurement of hydronephrosis in utero
- Affected by gestational age, maternal hydration, bladder distension
- Thresholds:

Degree of ANH	Second Trimester	Third Trimester	% of ANH
Mild	4-7 mm	7-9 mm	56-88
Moderate	7-10 mm	9-15 mm	10-30
Severe	>10 mm	> 15 mm	2-13

AP Diameter



AP Diameter

- Risk of postnatal pathology based on antenatal AP diameter

Pathology	Mild ANH	Moderate ANH	Severe ANH
UPJ obstruction	4.9%	17%	54.3%
VUR	4.4%	14%	8.5%
PUV	0.2%	0.9%	5.3%
UVJ obstruction	1.2%	9.8%	5.3%
Other	1.2%	3.4%	14.9%

- Increased incidence of postnatal pathology based on severity of ANH except for VUR

SFU Grading System

- Developed by the Society of Fetal Urology in 1993
- 5-point grading system based on postnatal sonographic appearance
 - Grade I: Pelvic splitting, normal parenchymal thickness
 - Grade II: Pelvic dilation, normal parenchymal thickness
 - Grade III: Pelvic ectasia, normal parenchymal thickness
 - Grade IV: Pelvic ectasia, parenchymal thinning

SFU Grading of Infant Hydronephrosis

	Picture of renal cross splitting	IVP Appearance	Ultrasound Variants			
SFU Grade 0	No splitting					
SFU Grade 1	Ureter in pelvis barely splits area					
SFU Grade 2	Ureter fills intrarenal pelvis					
SFU Grade 3	Ureter fills extrarenal pelvis; major calyces dilated					
SFU Grade 4	SFU Gr 2 and minor calyces ectatically dilated and parenchyma preserved					
SFU Grade 5	SFU Gr 3 and parenchyma thin					

Figure 3 The Society for Fetal Urology Hydronephrosis Grading System (http://www.uab.edu/images/peduro/SFU/sfu_grading_on_web/sfu_grading_on_web.htm).

UTD Classification

- Developed by consensus panel in 2014
- Goal to standardize pre- and post-natal imaging
- Based on:
 - AP Diameter
 - Calyceal dilation
 - Renal parenchymal thickness
 - Renal parenchyma appearance
 - Associated bladder and ureteral abnormalities

UTD Classification

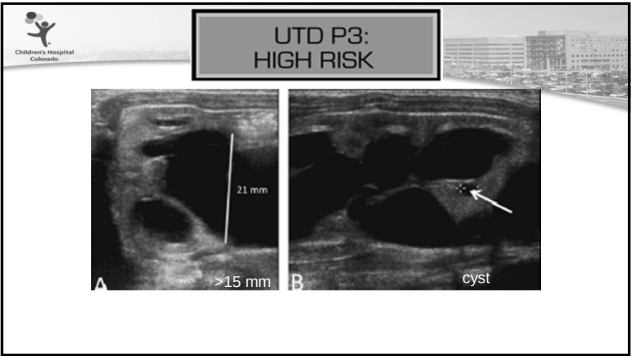
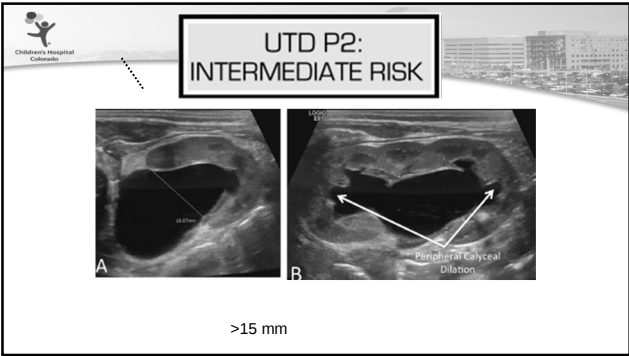
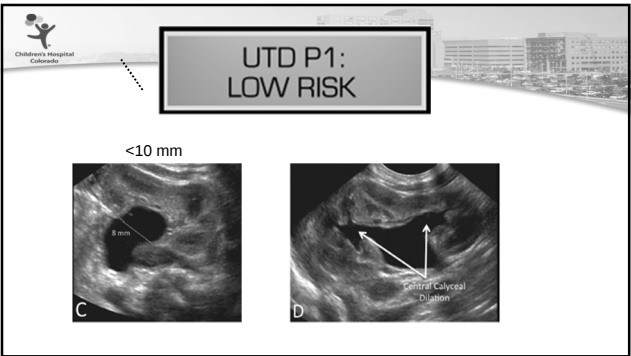
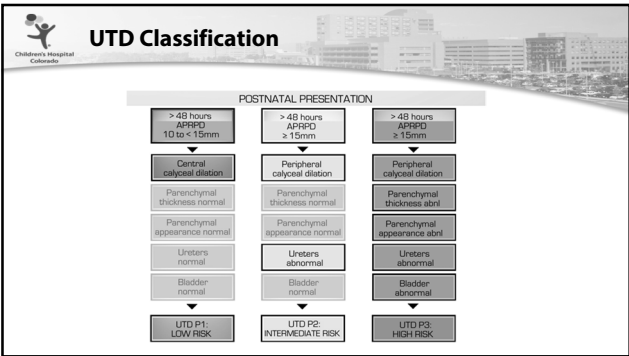
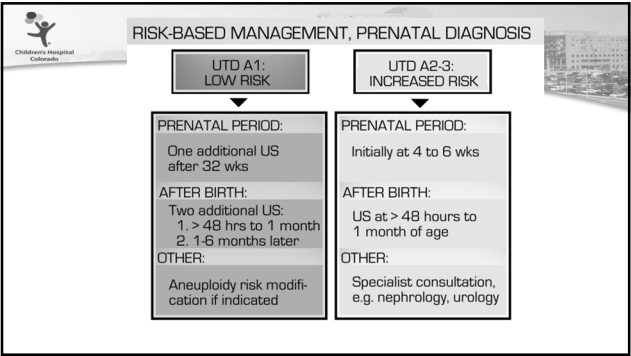
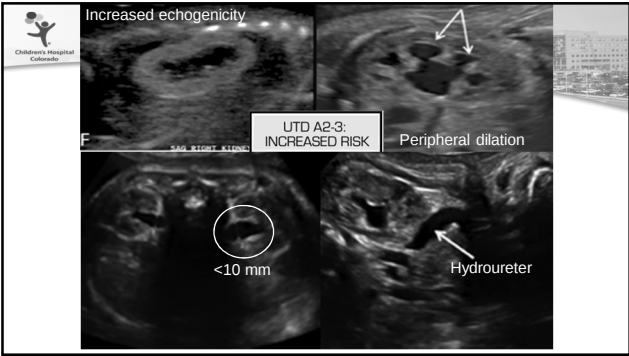
PRENATAL PRESENTATION	
16-27 wks AP-RPD 4 to <7mm	> 28 wks AP-RPD 7 to <10mm
Central or no calyceal dilation*	Peripheral calyceal dilation*
Renal parenchymal thickness normal	Renal parenchymal thickness abnl
Renal parenchymal appearance normal	Renal parenchymal appearance abnl
Ureters normal	Ureters abnormal
Bladder normal	Bladder abnormal
No unexplained oligohydramnios	Unexplained oligohydramnios**
UTD A1: LOW RISK	UTD A2-3: INCREASED RISK

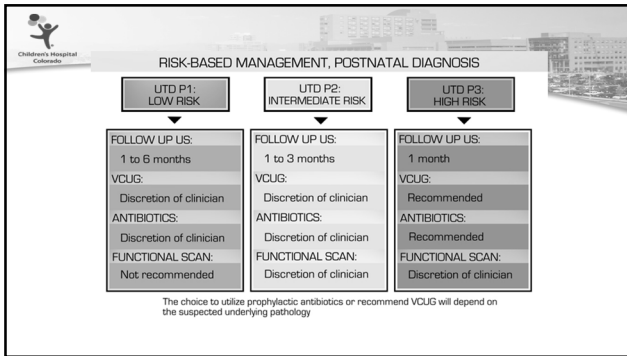
*Central and peripheral calyceal dilation may be difficult to evaluate early in gestation
**Unexplained oligohydramnios is suspected as result from a GU cause

GA 19 wk

GA 37 wk

UTD A1: LOW RISK





APD vs UTD (Prenatal)

APD Classification	Measurement	UTD Classification	Differences
Mild	4-7 mm	A1	Central dilation only
	7-9 mm		No oligohydramnios/ lower tract anomalies
Moderate	7-10 mm	A2-3	Peripheral dilation
	9-15 mm		Abnormal parenchyma
Severe	>10 mm		Associated lower tract anomalies
	>15 mm		Oligohydramnios

SFU vs UTD (Postnatal)

SFU Classification	Definition	UTD Classification	Differences (Renal)	Differences (LTA)
1	Pelvic splitting, normal parenchymal thickness	P1	APD 10-15 mm	No bladder or ureteral abnormality
2	Pelvic dilation, normal parenchymal thickness			
3	Pelvic ectasia, normal parenchymal thickness	P2	APD >= 15 mm	Ureteral abnormality
4	Pelvic ectasia, parenchymal thinning	P3	APD >= 15 mm Abnormal parenchymal appearance	Bladder or ureteral abnormality

- Post-natal evaluation**
- Resolution of hydronephrosis
 - Repeat ultrasound at 3-4 weeks to account for neonatal oliguria
 - SFU grades I-II
 - Tend to resolve
 - Ultrasound alone to monitor resolution
 - Rare cases of late progression and need for surgery
 - SFU grade III
 - 50% may ultimately require surgical intervention
 - Use of renography to assess timing and need for further studies
 - Normal renogram: ultrasound surveillance
 - Abnormal/indeterminate renogram: intervene or repeat renography
 - SFU grade IV
 - Highest risk of surgical intervention
 - Renography recommended to evaluate severity of pathology

Associated Pathology

UPJ obstruction
UVJ obstruction
Ureterocele
VUR
Posterior urethral valves

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Associated Pathology

36% of children with ANH have significant postnatal pathology

Diagnosis	Prevalence
Ureteropelvic Junction Obstruction	43%
Vesicoureteral Reflux	24%
Ureterovesical Junction Obstruction	12%
Posterior Urethral Valves	11%

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Transient Hydronephrosis

- Majority of children with ANH (41-88%)
 - Majority of cases with AP diameter < 6mm in second trimester
 - <40% of children with AP diameter <12 mm in third trimester
- May be due to:
 - high urine volume
 - transient UPJ obstruction
 - congenital ureteral folds



Ureteropelvic Junction Obstruction

- Most common finding is pelvicalyceal dilation without ureteral dilation
- 10-30% of children with ANH
- Risk of surgical intervention 38-52%
- Associated with other renal anomalies:
 - Vesicoureteral reflux
 - Multicystic dysplastic kidney



UPJ Obstruction - Symptoms

- Usually asymptomatic
- Dietl's crisis in the older child
- Rare
 - UTI/hematuria
 - Stones
 - UPJ disruption after trauma



Likelihood of Surgery

AP diameter	Percent undergoing surgery
<20 mm	1-3%
>20 mm	20%
>30 mm	55%
>40 mm	80%
>50 mm	100%



Renal Impairment

- Risk of renal deterioration

AP diameter	Functional deterioration
30-40 mm	84%
>40 mm	100%

- Suggests that initial AP diameter > 30 mm may be a relative indication for surgery



Role of Observation

- SFU grade III-IV hydronephrosis:

Outcome	Percent	Time to outcome
Resolution (SFU grade 0-I)	69%	19 months
Improvement (SFU grade II)	29%	30 months
Pyeloplasty*	22%	<18 months

*Indications for surgery: worsened hydronephrosis/decrease in function

Role of T 1/2

- T 1/2 does not predict likelihood of resolution

Outcome	T1/2 > 20 minutes (initial)	T1/2 > 20 minutes (follow up)
Improvement/Resolution	58%	33%
Increased hydronephrosis/functional deterioration	91%	37%

Indications for Surgery

Indication for surgery	Percent
Impaired renal function	40%
Absence of radiotracer clearance	6.7%
Worsened hydronephrosis/renal function	33.3%
Symptomatic presentation	10%
Parental preference	10%

Surgery for UPJ obstruction

- Pyeloplasty (gold standard)**
 - Most commonly used with a >95% success
 - Robotic/laparoscopic may have lower morbidity in children and adolescents
 - Stent/nephrostomy optional
- Endopyelotomy**
 - Lower success rates than in adults
 - May be good for postoperative obstruction

Outcomes

- Long term outcomes
 - 50-55% of infants with initial SFU grade 3-4 hydronephrosis will require pyeloplasty
- Long term outcomes for conservative management
 - 20%-35% may require delayed pyeloplasty
 - 1-2% will require pyeloplasty after age 4 years
- Long term surgical outcomes
 - 5 year follow up: 1.3% late obstruction rate
 - >10 year follow up: 4.1% late obstruction rate

UVJ Obstruction

- 5-10% of children with ANH
- Common findings of antenatal hydronephrosis and ureteral dilation with normal bladder
- Majority (70%) resolve spontaneously



Surgery for UVJ Obstruction

- Indications for surgery**
 - Progression of hydronephrosis
 - Loss of function
 - Symptomatic presentation (UTI, stone)
- Surgical approach**
 - Intravesical ureteral reimplant
 - 5:1 tunnel
 - Consider tailoring or plication if > 1 cm diameter



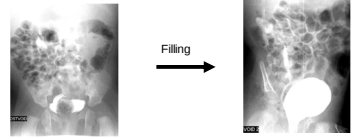
Ureterocele

- 1/1000 on autopsy studies
- M:F 1:5
- Duplex vs single system (5:1)
 - Associated with upper pole (Weigert-Meyer rule)
- 10% bilateral
- Common finding of antenatal hydronephrosis with associated cystic mass in bladder:
- May be associated with:
 - Bladder outlet obstruction
 - Intraital mass



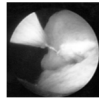
Ureterocele

- Post-natal imaging with US and VCUG
- Need for early and late filling images for diagnosis



Surgery for Ureterocele

- Cystoscopic incision
 - If orthotopic, low transverse & small
 - If ectopic, must open below the bladder neck
 - Associated with post-operative reflux in 50%
- Heminephrectomy
 - If minimal function, no reflux of lower pole moiety
- Ureteroureterostomy
 - If preserved function, no reflux of lower pole moiety
- Excision and common sheath reimplantation
 - If preserved function, associated reflux



All options associated with risk of future additional surgery

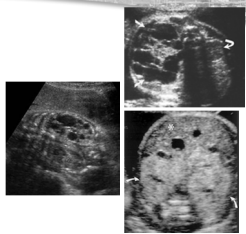
Multicystic Dysplastic Kidney

- Common findings of multiple non-communicating cysts without normal renal parenchyma
- 4-6% of children with ANH
- Renal length <62 mm on initial postnatal ultrasound associated with complete involution of the MCDK



Prenatal Findings

- MCDK: non-communicating cysts
- ARPK: bright, enlarged kidneys
- ADPK: enlarged kidneys with associated large cysts

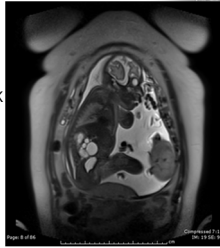


Treatment of MCDK

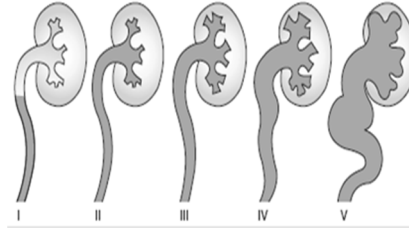
- Role of surveillance
 - Potential role for ultrasound surveillance until complete involution or age 4 years
 - Frequency of surveillance not clear
- Risks of conservative management
 - Wilms' Tumor
 - <0.05% risk of Wilms' Tumor
 - Majority (>70%) present prior to age 4 with associated palpable mass
 - No cases of malignancy in involuting MCDK
 - Hypertension
 - 0.5%-2% incidence of hypertension
 - Nephrectomy may not be curative

Surgery

- Indications for surgery
 - Suspected MCDK with atypical solid or functional components
 - No clear evidence for prophylactic nephrectomy in non-functional MCDK



Vesicoureteral Reflux



Incidence

- Overall incidence of 0.4-1.8%
 - 10 times more common in Caucasians
- Antenatal hydronephrosis:
 - 24% incidence of associated vesicoureteral reflux
 - Independent of degree of hydronephrosis
- Febrile UTI
 - 25-40% with associated reflux
- Family history
 - Siblings 30-50%
 - Offspring 60-70%

Etiologies of Reflux

- Primary
 - Immature ureterovesical junction
 - Maldevelopment of ureterovesical junction
 - High pressure voiding in infancy
- Secondary
 - Neurogenic bladder
 - Dysfunctional elimination syndrome with associated high pressure during storage and/or voiding
 - Bladder outlet obstruction (e.g., posterior urethral valves)
 - Connective tissue disorders

Natural History

- Resolution rate of reflux in infants with asymptomatic antenatal hydronephrosis 59.2% (vs 49.9% for all infants)
- Equivalent rate of resolution in boys and girls
- Mild-moderate reflux (grades I-III) with higher likelihood of resolution than severe reflux (grades IV-V) (71% vs. 28%)

Recurrent Febrile UTI

- Increased risk of recurrent febrile UTI with higher grades of vesicoureteral reflux

	Recurrence rate
No reflux	18.5%
Grade I	33.3%
Grade II	18.5%
Grade III	44.2%
Grade IV	50%



Renal Scarring

- Associated with higher grades of reflux
- May be more prevalent in girls

Reflux Grade	Progression of scar	New Scar
No reflux	0	0
I	0	0
II	0	2.3%
III	4.0%	5.8%
IV	7.2%	6.0%



Chronic Kidney Disease

- 15% incidence of renal insufficiency in children with reflux
- Most common etiology for end stage kidney disease in children
 - 1/6000 children with reflux will develop end stage kidney disease
- Slower progression to ESRD than other causes of chronic kidney disease
 - Primary bilateral high grade reflux in the first year of life associated with increased risk of progression
 - Febrile UTI may be associated with increased rate of progression but not increased risk of progression



SFU Guidelines

Degree of unilateral ANH	Results of postnatal US	Recommendation for VCUG
Mild	Resolved Grade I/II Grade III/IV	No No/Yes Yes
Moderate	Resolved Grade I/II Grade III/IV	No Yes Yes
Severe	Resolved Grade I/II Grade III/IV	Yes Yes Yes

- Recommended within the first week of life if bilateral moderate or severe ANH, dilated ureter, ureterocele, or concern for other lower urinary tract pathology



Continuous Antibiotic Prophylaxis

- Based on the premise that a large percent of reflux resolves and that prophylaxis prevents UTI and renal damage while awaiting resolution
- Cochrane Database Review
 - Meta-analysis of 11 studies

	Antibiotics vs. Observation
UTI	RR=0.75 (95%CI 0.15-3.84)
Renal Damage	RR=1.70 (95% CI 0.36-8.07)



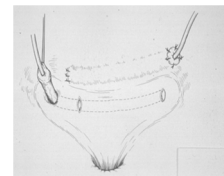
Surgery

- 17.7% of infants initially treated with continuous antibiotic prophylaxis will have subsequent surgical treatment
- Indications for surgery:
 - Breakthrough UTI
 - Treatment noncompliance
 - Poor renal function/associated renal dysplasia
 - Progressive renal damage/scar formation
 - Persistent grade IV-V reflux
 - Parental preference



Ureteral Reimplantation

- Gold Standard
 - 95-99% Success Rate
- Multiple Approaches
 - Intravesical
 - Extravesical
 - Laparoscopic/Robotic
- Potential for Obstruction (2%)
 - Ureteral kinking/scarring



Endoscopic Treatment

Advantages

- Technically easy
- Low morbidity

Disadvantages

- Success rate
- Recurrence rate



AUA Recommendations

- Initial evaluation of the child with febrile UTI**
 - Urine culture
 - Renal ultrasound
 - DMSA optional to evaluate for pyelonephritis/scar
- Follow up evaluation**
 - Annual urinalysis
 - VCUG and US every 12-24 months
 - Option of no VCUG in children treated with observation alone who remain asymptomatic
 - DMSA where there is an abnormality on ultrasound, breakthrough UTI, severe reflux (Grade III-V), or elevated serum creatinine

AUA Recommendations

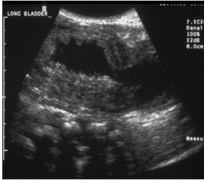
- Antibiotic Prophylaxis**
 - Infants with reflux and history of febrile UTI due to associated morbidity
 - Infants with grade III-V reflux
 - Option for the child > 1 year with history of UTI and reflux in the absence of bowel/bladder dysfunction
- Breakthrough UTI**
 - If not on prophylaxis, recommend initiation of antibiotic prophylaxis
 - If on prophylaxis, recommend surgical intervention
 - Option of antibiotic switch if single breakthrough UTI on prophylaxis
- Management following resolution of reflux**
 - Monitor blood pressure, height, weight, urinalysis if renal scarring

AUA Recommendations

Patient Age	Febrile UTI	Reflux grade	Initial Management	Indication for Surgery
< 1 year	No	I-II	Observation or antibiotics; consider circumcision	Breakthrough UTI
< 1 year	No	III-V	Antibiotics; consider circumcision	Breakthrough UTI
< 1 year	Yes	I-V	Antibiotics; consider circumcision	Breakthrough UTI
> 1 year	Either	I-V	Antibiotics if renal scar, recurrent UTI	Initial vs breakthrough UTI

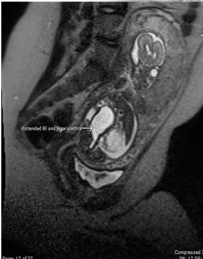
Posterior Urethral Valves

- Associated with:**
 - Antenatal hydronephrosis (unilateral or bilateral)
 - Thickened, dilated bladder that does not empty
 - Dilated posterior urethra
 - Oligohydramnios
- 1:5000-8000 male births
- Diagnosis associated with pulmonary hypoplasia and chronic renal failure



Prenatal Evaluation

- Fetal Karyotype**
 - Confirm 46 XY
 - Consider cloacal anomalies if XX
 - Reports of trisomy 21, 18, and Klinefelter syndrome
 - 5% aneuploidy rate
- Ultrasound**
 - Assess other anomalies
 - Neural tube defects
 - Cardiac defects
 - Evolving role of MRI
- Fetal vesicocentesis**
 - Evaluate renal function
 - ?Repeat sample after 24-48 hours



Prenatal US Findings

- Male
- Bilateral hydronephrosis
- Oligohydramnios
- Bright Kidneys
 - sensitivity 0.57
 - specificity 0.84



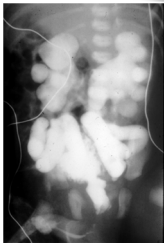
Fetal Urinary Electrolytes

Prognostic values:

	Good Prognosis	Poor Prognosis
Sodium	<90 mmol/L	>100 mmol/L
Chloride	<80 mmol/L	>90 mmol/L
Osmolality	<180 mOsm/L	>200 mOsm/L
Calcium	<7 mg/dL	>8 mg/dL
Protein	<20 mg/dL	>40 mg/dL
β2-Microglobulin	<6 mg/L	>10 mg/L

Postnatal Diagnosis: VCUG

- Dilated, elongated posterior urethra
- Trabeculated bladder
- Vesicoureteral reflux



In Utero Intervention

- Indications:
 - 20-32 weeks
 - Favorable electrolytes
- Interventions
 - Vesicoamniotic shunt
 - Valve ablation
 - Amnio-infusion
- Outcomes
 - High risk of premature delivery
 - Often require multiple interventions
 - Helps lungs, but may not impact renal or bladder function



Postnatal Management

- Early Intervention
 - Stabilize electrolytes and monitor creatinine
 - Catheter placement (5 Fr)
 - Endoscopic ablation (>3500 gm)
 - Vesicostomy if small/premature
 - Ureterostomy if secondary UVJ obstruction
- Long-term Outcomes
 - Renal function
 - Chronic renal failure in 17-40% of adolescents
 - Predictors:
 - Creatinine nadir
 - Bladder dysfunction
 - Bladder function
 - UDS
 - May need CIC
 - May need overnight drainage due to polyuria

VURD Syndrome

- Valves
- Unilateral Reflux
- Renal Dysplasia
- Hypothesized to improve prognosis (pop-off) but results mixed





Conclusions

- Antenatal hydronephrosis is a common finding associated with a wide spectrum of disease processes
- Goal of treatment is renal preservation
- Majority of children will not require surgical intervention
 - Higher risk of surgery in cases of more severe hydronephrosis
 - Higher rates of postnatal pathology with worsening or new onset hydronephrosis in the third trimester



Conclusions

- Ultrasound alone may not be sufficient to determine diagnosis or benefit of surgery
- Nuclear renography may be a helpful adjunct
 - Differential function < 40% or worsening function associated with surgical benefit
 - T ½ is not a good predictor of outcome
- Role of VCUG remains controversial
 - VCUG is recommended for:
 - Higher grades of hydronephrosis
 - Suspicion of associated lower tract pathology
 - Benefit not clear in low grade hydronephrosis



Referral to Pediatric Urology?

- Infants at risk for underlying renal/bladder pathology
 - Infants with unilateral or bilateral grade 3 or 4 hydronephrosis
 - Infant boys with bilateral grade 2 hydronephrosis
- Early referral (within first week of life) if:
 - Infant boy with suspected PUV
 - Infant with ureterocele especially if associated bilateral hydronephrosis or bladder outlet obstruction
- Infants with isolated grade 1 or unilateral grade 2 hydronephrosis do not need routine referral unless:
 - Associated high grade reflux
 - Associated renal dysplasia
 - Worsening hydronephrosis



Thank You




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Children's Hospital Colorado

Common Pediatric Urological Conditions-Kidneys, Genital Tract

J Todd Purves MD PhD

Disclosures

- None

Section 1: Genitalia

- Male
 - Foreskin: elective circumcision, phimosis, penile adhesions, balanitis, BXO
 - Meatal Stenosis
 - Hypospadias/Chordee
 - Cryptorchidism/Retractile Testes
 - Hydroceles
- Female
- Disorders of Sexual Differentiation

Elective Circumcision

“Although health benefits are not great enough to recommend routine circumcision for all male newborns, the benefits of circumcision are sufficient to justify access to this procedure for families choosing it and to warrant third-party payment for circumcision of male newborns.”

-2012 American Academy of Pediatrics
Circumcision Policy Statement

Pediatrics 150(3): Sept 2012

Risks/Benefits

- Benefits
 - Lower risk of UTI (particularly in 1st year)
 - Decreased STD transmission rates including HIV
 - Lower risk of penile cancer
- Risks
 - Infection
 - Bleeding
 - Injury
 - Anesthetic risks
 - Poor cosmesis

Indications for Circumcision

- Recurrent balanitis/Balanitis Xerotica Obliterans
- Phimosis that restricts voiding or results in painful erections
- Obstructive uropathy
- Vesicoureteral Reflux

Relative Contraindications

- Bleeding disorders (e.g., hemophilia, Von Willebrand's, etc.)
- Medical co-morbidities that increase anesthetic risks (e.g., cardiac, pulmonary disease)

Methods of Circumcision

- Office techniques: Plastibell, Gomco clamps
 - Newborns (up to 3 months) with normal penile anatomy
- Surgical techniques: Tube sleeve
 - > 3 months of age or too large for clamps
 - Penile anomalies (loose penile shaft skin, buried penis, chordee, glanular hypospadias/megameatus where urethral correction not warranted)
 - Comorbidities best managed in the OR

Buried Penis/Loose Shaft Skin



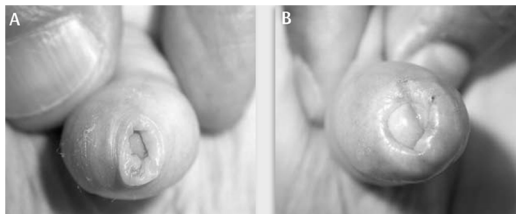
Hadidi H J Ped Surg 49(2): 374-9. 2012

- Best managed with surgical circumcision/phalloplasty

Phimosis

- Prepuce is non-retractile during neonatal development
- Up to 10% of 3 year olds have non-retractile foreskin
- Pathological phimosis: non-retraction is due to distal cicatrix/scarring
- Problems: obstruction of urinary stream, pain with retraction, balanitis, BXO
- Non-problematic phimosis should be allowed to resolve with time and proper hygiene

Physiological versus Pathological Phimosis



McGregor T, Pike J, and Leonard M Can Fam Physician 53(3): 445-8. 2007

Treatment of Phimosis

- Asymptomatic cases should be given time to resolve, using good hygiene
- 6-8 weeks of topical steroids (Betamethasone or Triamcinolone cream applied BID)
- Circumcision

Penile Adhesions

- Uncircumcised boys
 - Present as foreskin separates from glans
 - May result after forcefully retracting glans
- Circumcised boys
 - Penile shaft skin adheres to glans, most common with large pubic fat pad
 - May form keratinized skin bridge(s)

Treatment of Penile Adhesions

- Asymptomatic, non-keratinized adhesions may be treated with proper hygiene and gentle retraction
- If painful: blunt lysis if very mild, topical steroids for 6-8 weeks
- Keratinized skin bridges require sharp lysis
- If due to incomplete circumcision, revision of the circumcision may be necessary.

Penile Adhesions



Non-keratinized. May treat with good hygiene with gentle retraction if asymptomatic. Steroid cream or blunt lysis if symptomatic.



Keratinized skin bridges. Requires surgical excision.

Krill AJ, Palmer LS and Palmer JS Scientific World Journal

Balanitis/BXO

- Balanitis often caused by bacteria, Candida spp., or systemic skin conditions
- Immediate treatment of balanitis: topical or oral antibiotics (erythromycin or penicillin), antifungals (clotrimazole or miconazole), steroid cream therapy (hydrocortisone)
- Balanitis xerotica obliterans: chronic inflammation, male genital variant of lichen sclerosis. Treat with circumcision

Balanitis/BXO

Balanitis



Huang CJ Clin Ped Emerg Med
10: 56-9. 2009

BXO



Celis S, et al J Ped Urol 10(1): 34-39. 2014

Meatal Stenosis

- Anatomically (<5Fr) in up to 20% circumcised boys
- Symptomatic in 3-8% of circumcised boys
- Trauma to exposed urethral epithelium (prevent with topical lubricant for 6 mos after circumcision)
- Narrowing of meatus
- Spraying or upward deviation of urinary stream
- Obstruction with straining.
- Dysuria
- Voiding issues/incontinence

Meatal Stenosis



Persad R, et al BJU 75: 91-3. 1995

Meatotomy versus Meatoplasty

- Meatotomy: simple vertical incision of ventral scarring under local anesthesia. No suturing.
 - May be done in office without general anesthesia.
 - Frequently not tolerated by children.
 - Higher re-stenosis rate (3.5%) than meatoplasty¹.
- Meatoplasty: vertical incision of ventral scarring plus stitching of urothelial edge to epithelium
 - Requires general anesthesia in the OR.
 - Less psychological trauma in children
 - Lower re-stenosis rate (0.2%) than meatotomy¹.

1. Godley SP et al J Pediatr Urol 11(1): 38.E1-38.E6. 2015

Priapism

- Ischemic priapism far more common in children than non-ischemic priapism
- Stuttering priapism common in children with sickle cell disease
- Most common etiologies for pediatric priapism: sickle cell disease (65%), leukemia (10%), trauma (10%), idiopathic (10%), and pharmacological (5%)

Neonatal Priapism

- Extremely rare. Idiopathic but hypothesized to be due to perineal trauma during delivery
- Presence of fetal hemoglobin prevents neonatal priapism in sickle cell disease
- Zero reports of necessity for corporal injection or surgical intervention
- Observation appropriate

Evaluation of Pediatric Priapism

- History must be taken and relevant blood testing (CBC, hemoglobin S) performed to uncover etiology
- Absence of pain is unreliable indicator of non-ischemic priapism.
- Color duplex ultrasonography: Frog legged position. Ischemic if high resistance, low velocity wave form with absent or low arterial flow. Close to 100% specificity and sensitivity.
- Corporal blood gas(obtained at aspiration): Ischemic priapism will show hypoxia, acidosis, hypercarbia. Glucopenia correlates with tissue damage.

Treatment of Pediatric Priapism

- Management algorithms similar to adults
- Regardless of etiology, immediate relief of ischemia is paramount to prevent damage
- Anesthesia: Opiates useful for pain control of ischemic priapism and also a detumescent. Conscious sedation with local anesthesia most useful in children. Ketamine, in dissociative sedation, is a detumescent.
- Corporal aspiration/lavage: Lateral midshaft corporal needles placed at 3 and 9 o'clock. Prepubescent boys use 21 or 23G butterfly, Postpubescent use 19G. May need larger needle for clots. Hold pressure 5 minutes after removal to prevent hematoma.

Treatment of Pediatric Priapism

- Intracorporal injection: AUA guidelines don't cover pediatric dosing. Monitor with telemetry, BP, HR and Pulse Ox)
 - Older than 10 yrs: Up to 10x 0.5mL aliquots of 200µg/mL phenylephrine¹
 - 2-10 yrs: Irrigation up to 4x with 10mL of 1:1,000,000 epinephrine²
- As per adults, failure after ICI proceeds to shunting.

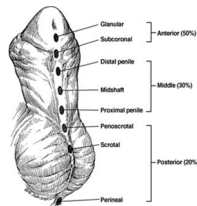
¹ Donaldson, JF, Rees RW, and Steinbrecher HA J Pediatr Urol 10(1):11-24. 2014
² Mantadikis E, et al Blood 95(1): 78-82. 2000

Special Concerns for Sickle Cell Patients

- 30% of patients with SCD experience ED due to priapism
- Adjunct therapies (hyperhydration, supplemental oxygen, plasma alkalization, plasmapheresis and analgesia) should not delay corporal aspiration
- Stuttering priapism: teach 1st aid methods (exercise, urination, cold bath, ejaculation) and encourage seeking tx if longer than 2 hours, oral sympathomimetic (alpha agonists such as pseudoephedrine 0.5mg/kg QHS, PDE-5 inhibitors but not acutely, hydroxyurea 10-35mg/kg/day)

Hypospadias

- Ventrally displaced urethral meatus, ventral chordee, dorsally hooded foreskin
- 1 in 250 male births in USA
- Etiology due to genetic, endocrine and environmental factors but largely unknown



Kraft KH, Shukla AR and Canning DA
 Urol Clin North Am 37(2): 167-81. 2010

Evaluation of Hypospadias

- Typically diagnosed at child's first exam.
- When diagnosed during circumcision, complete the procedure.
- Assess location and patency of meatus, severity of chordee, size of penis
- Severe hypospadias or hypospadias and cryptorchidism warrant karyotype and DSD workup

Associate findings

- Hernia/Cryptorchidism-DSD workup
- DSD-27% in boys with hypospadias and UDT
- Enlarged prostatic utricle- more common in severed hypospadias. Consider when boys present with epididymitis, urethral stone or are difficult to catheterize.

Goals of Treatment

- Glanular meatus to allow voiding in standing position. Properly positioned ejaculate for fertility.
- Straight penis to allow sexual function.
- Cosmesis with conical glans and supple penile shaft skin

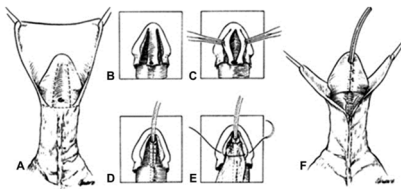
Androgen Stimulation

- Boys with stretched penile length below 3rd percentile or too small for reconstruction may require androgen stimulation
- No standard of treatment
- Common strategy is for 25mg testosterone enanthate IM injection 6 and 2 weeks prior to surgery
- Some advocate earlier administration to decrease bleeding

Types of Hypospadias Repair

- Distal: Meatal advancement and glanuloplasty
- Distal and Proximal: Tubularized incised plate urethroplasty
- Proximal: Island onlay hypospadias repair (useful for narrow urethral plate), Transverse island tube repair (useful with more severe chordee), Two stage repair (1st: scrotoplasty, chordee repair often with transection plate, Byar's flaps. Approximately 6 months later, 2nd: tubularize urethra to glans, complete repair)

Tubularized Incised Plate Urethroplasty



Snodgrass TW Urology 54(1): 6-11

Tips for the TIP

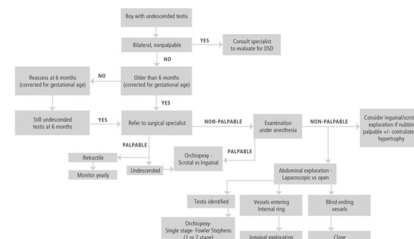
- Width of urethral plate, after incision, must accommodate 6 Fr catheter
- Midline incision of plate down to corporal bodies
- Do not extend distal to plate to avoid meatal stenosis
- Tubularize urethra with 2 layer subcuticular closure using 6-0 polyglactin over 6-8 Fr stent
- Cover urethroplasty with dartos flap. Tunica vaginalis flap if dartos not available.
- Compression dressing and keep stent approximately one week

Complications of Hypospadias Repair

- Overall complication rate for midshaft to distal hypospadias about 10%
- Fistula: observation for 6 months for healing and possible spontaneous resolution. Then simple or complex repair.
- Strictures: Dilation and DVIU possible for very mild cases. Frequently, excision of repair and buccal grafting with subsequent repair needed.
- Meatal stenosis/diverticuli: cystoscopy to assess obstruction
- Recent literature suggests higher rates of complications than previously reported.

Cryptorchidism/Retractile Testes

- Evaluation and management of undescended testes should follow the 2014 AUA guidelines¹



1 Kolon TF et al J Urol 192(2): 337-45. 2014

Evaluation of Cryptorchidism

- Testicles descend into scrotum during 3rd trimester
- 3% of boys born with UDT, 1% at one year
- Testosterone surge at 1 to 3 months of age
- Undescended testes should be treated at 6 months corrected for gestational age
- UDT and hypospadias or bilateral UDT prompt workup for disorders of sexual differentiation
- Imaging not useful

Retractile Testes

- Testes have descended
- Strong cremasteric reflex: cold, fear, touch
- Ask parents/caregivers if they see testes in scrotum during bathing/diaper changes
- Reflex diminishes at puberty-No Surgery!
- Some small risk of ascent- annual examination

Cryptorchidism Treatment

- No role for hormonal therapy
- Exam under anesthesia to identify position and plan surgical approach
- Palpable testes undergo open inguinal or scrotal (Bianchi) approach
- Non-palpable testes on EUA require diagnostic laparoscopy/abdominal exploration
- Primary orchidopexy most successful (96%) but not always possible. 1 (79%) or 2 (86%)stage Fowler Stephens for short vessels.
- Testicular vessels must be identified for diagnosis of vanishing testis

Long Term Consequences of UDT

- Higher risk of testis cancer. Earlier reports may have overestimated risk.
- Orchidopexy prior to puberty decreases risk
- Paternity rates for a) no UDT 94%, b) unilateral UDT 90% and c) bilateral UDT 62%
- Orchidopexy prior to 18 months of age may help preserve fertility
- Testis biopsy may have use in predicting fertility but is limited in clinical use
- Cosmesis

Hydroceles

- Overwhelming majority of pre-pubertal hydroceles are communicating
- Communicating hydroceles result from migration of peritoneum during testis descent
- No abdominal wall defect, treat with high ligation
- In term infants, surgery delayed 18-24 months to allow spontaneous closure of tunica vaginalis
- Premature infants at higher risk of developing strangulated hernia and so repaired urgently

Vaginal Masses

- Paraurethral cysts or Skene's cysts
- Prolapsed ureterocele
- Urethral prolapse
- Rhabdomyosarcoma

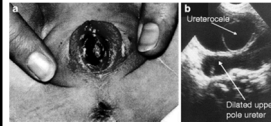
Paraurethral cysts (Skene's cysts)

- Presents in infancy as smooth whitish paraurethral mass
- Most rupture/resolve in a few months without intervention
- If symptomatic with urinary spraying or persistent, simple excision or needle aspiration



Fujimoto T et al J Ped Surg 42(2): 400-3. 2007

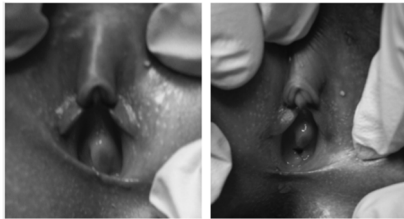
Prolapsed ureterocele



Hurwitz R.S. (2010) Disorders of the Female External Genitalia. In: Godbole P., Koyle M., Wilcox D. (eds) Guide to Pediatric Urology and Surgery in Clinical Practice. Springer, London

- Large purplish mass in vestibule, eccentric
- Associated with upper pole of dilated system
- Can cause urinary obstruction, UTI
- Renal/bladder ultrasound to aid diagnosis

Urethral Prolapse



Nguyen K and Jacobs K
Consultant 15(3):138-9.
2016

- Circumferential protrusion of urethra
- Presents with bloody spotting; dysuria/pain
- African American girls 4-5 years
- 1) Sitz baths, treat constipation 2) conjugated estrogen cream 3) surgical excision

Vaginal Rhabdomyosarcoma



<https://web.duke.edu/pathology/bones/bones2016.html>

Labial adhesions



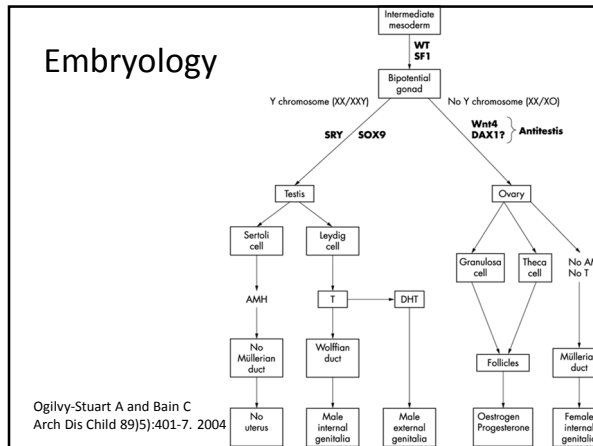
- Common 3 months-3 years
- Asymptomatic, voiding problems (dribbling), UTI
- Asymptomatic should be observed. Up to 80% resolve in one year
- Girls in diapers have high recurrence after treatment
- Conjugated estrogens or estradiol cream (Estrace) bid for 2-6 weeks
- Gentle blunt lysis with Q tip and lubricant. In OR or office with EMLA anesthesia

Syed-Ansari T, et al Glob libr women's med
(ISSN:1756-2228) 2008; DOI 10.3843/GLOWM.10010

Disorders of Sexual Development

- Embryology
- Nomenclature
- Gender Assignment
- Surgical Management
- Gonadal Tumors
- Hormone Replacement
- Psychosocial Issues

Embryology



Disorders of Sexual Differentiation

- 2006 Revision of Nomenclature

Previous	Current
Intersex	DSD
Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinization of an XY male	46,XY DSD
Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Lee PA et al Pediatrics 118(2): E488-500. 2006

DSD Classification

Sex Chromosome DSD	46,XY DSD	46,XX DSD
45,X (Turner syndrome and variants)	Disorders of gonadal (testicular) development: (1) complete gonadal dysgenesis (Swyer syndrome); (2) partial gonadal dysgenesis; (3) gonadal regression; and (4) ovotesticular DSD	Disorders of gonadal (ovarian) development: (1) ovotesticular DSD; (2) testicular DSD (eg, SRY*, duplicate SOX9); and (3) gonadal dysgenesis
47,XXY (Klinefelter syndrome and variants)	Disorders in androgen synthesis or action: (1) androgen biosynthesis defect (eg, 17-hydroxysteroid dehydrogenase deficiency, 5αRD2 deficiency, STAR mutations); (2) defect in androgen action (eg, CAIS, PAIS); (3) luteinizing hormone receptor defects (eg, Leydig cell hypoplasia, aplasia); and (4) disorders of anti-Müllerian hormone and anti-Müllerian hormone receptor (persistent Müllerian duct syndrome)	Androgen excess: (1) fetal (eg, 21-hydroxylase deficiency, 11-hydroxylase deficiency); (2) fetoplacental (aromatase deficiency, POR [P450 oxidoreductase]); and (3) maternal (luteoma, exogenous, etc)
45,X/46,XY (MGD, ovotesticular DSD)		Other (eg, cloacal exstrophy, vaginal atresia, MURCS [Müllerian, renal, cervicothoracic] somite abnormalities), other syndromes
46,XX/46,XY (chimeric, ovotesticular DSD)		

Lee PA et al Pediatrics 118(2): E488-500. 2006

Indications for DSD Evaluation (Newborn)

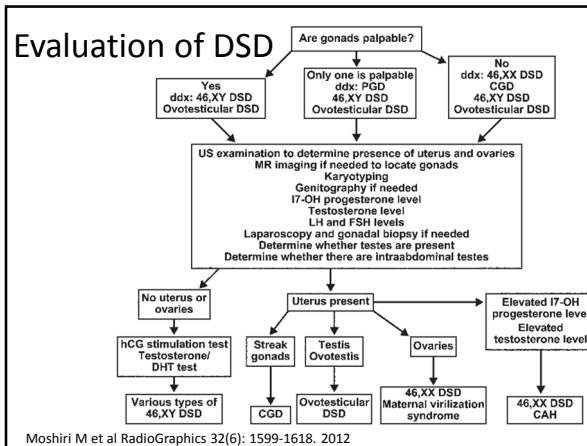
- Ambiguous genitalia
- Apparent female with clitoromegaly, posterior labial fusion, inguinal/labial mass
- Apparent male with bilateral UDT, micropenis, perineal hypospadias, any hypospadias with UDT
- Family history
- Discordance between phenotype and karyotype

Indications for DSD Evaluation (older children and young adults)

- Delayed/incomplete puberty
- Failure to initiate menarche
- Virilization of female
- Inguinal hernia in females
- Gynecomastia in males
- Cyclic gross hematuria in males
- Newly recognized genital ambiguity

Ambiguous Genitalia

- Emergent condition in newborn
- Most common diagnosis is congenital adrenal hyperplasia due to 21 hydroxylase deficiency
- Failure to recognize and treat electrolyte imbalances can be fatal



Gender Assignment

- Very controversial
- Do not rush! Avoid definitive statements prior to full evaluation.
- Factors include: Etiology/diagnosis, appearance and function of genitalia, surgical options, hormone replacement requirements, fertility, family/culture
- Current understanding and practice often leads to incorrect outcomes

Hormone Replacement

- Hypogonadism: gonadal dysgenesis, errors in sex-steroid biosynthesis, androgen insensitivity
- Hormonal replacement to initiate puberty: induce secondary sexual characteristics, overall growth, optimal bone development
- Males: intramuscular depot testosterone, oral testosterone undecanoate, transdermal
- Females: estrogen supplements, progestin started after 1-2 years of continuous estrogen OR development of breakthrough bleeding
- Pediatric endocrinology

Surgical Management

- Trend towards delaying surgery until consent from patient is possible
- Early “normalization” versus uncertainty
- Functional concerns may prohibit delay
 - Cloacal anomalies repaired to prevent infection, urinary obstruction, allow continence
 - Vaginoplasty to allow egress of menses
 - Symptomatic Mullerian remnants
 - Retained testicular tissue will cause virilization in children raised as females
 - Retention of testicular tissue can negatively impact fertility in cases of bilateral ovotestes
- Penile reconstruction pre vs post puberty
- Concerns about malignancy

Gonadal Tumors

- Testicular cancer risk highest in patients with Y chromosomal material, abdominal gonads, gonadal dysgenesis/streak gonads
- Dysgenetic gonads/streak gonads risk pre-pubertal malignancy-removed early
- PAIS with abdominal testes may have cancer risk as high as 50%
- CAIS very low risk of pre-pubertal malignancy and may benefit from hormonal production from native testes
- 46 XX DSD patients without Y chromosomal material-no increased risk

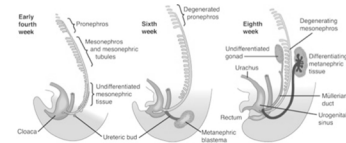
Psychosocial Issues

- DSD patients experience high rates of depression, anxiety, suicidal ideation, suicide attempts
- Gender identity
- Gender role
- Sexual Orientation
- Critical to enlist psychologists/psychiatrists with relevant expertise
- Address needs of both patients AND parents
- Trends towards earlier disclosure

Section II: Kidneys

- Embryology
- Renal agenesis/Duplication
- Ectopic kidney
- Ureteropelvic Junction Obstruction
- Cystic kidney disease
- Nephrolithiasis

Upper Tract Embryology



Doherty GM Current Diagnosis and Treatment: Surgery, 13th edition: <http://www.accessmedicine.com>

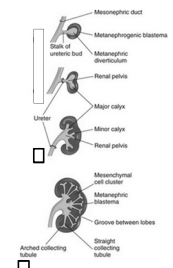
- Pronephrosis involutes by 4th week
- Mesonephrosis: principal excretory organ 4-8 weeks, then degenerates
- Metanephros: Originates from intermediate mesoderm and mesonephric duct as ureteric bud.

Development of the ureter

- Pronephric duct forms from anterior pronephric tubules and then serves as mesonephric duct, giving rise to ureter.
- Independent caudal growth of nephric duct to the cloaca.
- Ureter is outgrowth of nephric duct while renal tubules arise from adjacent metanephric blastema

Development of Kidney

- Cephalad growth of ureteric bud, contacts mesoderm of nephrogenic cord
- Metanephric cap enlarges and undergoes differentiation to form nephrons
- Ureteral bud expands to form renal pelvis and outpouchings to form primary collecting ducts
- Rotation so renal pelvis faces anteriorly



Moor KL and Persaud TVN. The urogenital system. In: Before we are born: essentials of embryology and birth defects. 7th ed. Philadelphia: Saunders Elsevier; 2003

Renal Agenesis

- Usually results from failure of ureteric bud to develop. Less likely involution of dysplastic kidney.
- Ipsilateral ureter and hemitrigone also absent.
- Defect may also affect other mesonephric duct derivatives: seminal vesicles, vas deferens (can be bilateral), and epididymis.
- Prognosis of unilateral agenesis excellent though some suggestion of increased renal dysfunction, proteinuria and HTN
- Bilateral renal agenesis incompatible with life. Only anecdotal survival beyond newborn period

Anomalies Associated with Unilateral Renal Agenesis

- 30-70% overall
- Vesicoureteral reflux: 28-41%
- Ureterovesical obstruction: 11-18%
- Ureteropelvic junction obstruction: 6-7%
- Can also affect heart, GI tract, genital and skeletal systems
- Higher incidence of single umbilical artery

Renal Duplication

- Overexpression of glial cell –derived neurotrophic factor (GDNF)-RET induces multiple ureteral bud formation
- If ureteric bud bifurcates prior to effacing metanephrosis-incomplete duplication with common distal ureter results
- Creation of two ureteric buds results in complete duplication

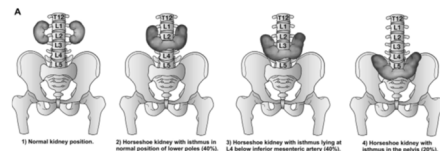
Consequences of Duplicated Kidney

- Often an inconsequential variant of normal
- Weigert-Meyer rule
 - Lower pole: ureter inserts cephalad to upper pole. VUR is common. Obstruction less common, usually UPJ and less likely at UVI
 - Upper pole: ureter inserts caudal to lower pole. Can be ectopic and insert into (boys) bladder, prostatic urethra or Wolffian structures such as seminal vesicles, ejaculatory ducts, epididymis or vas deferens while in girls into the bladder, urethra or vagina
- Ectopic ureter always above external sphincter in boys but either above/below in girls
- Ureterocele common at upper pole insertion

Ectopic Kidney

- Simple ectopy: failure to ascend normally.
- Crossed ectopy: with or without fusion
- Renal fusion: fusion of the metanephroi prior to ascent results in horseshoe or crossed fused ectopia. Ureteral orifices are orthotopic.
- Ectopic kidney may be clinically inconsequential. Higher risk of obstruction due to aberrant vessels, kinking due to malrotation. Hydronephrosis, stone and infection more common.

Horseshoe Kidney



Taghavi K, Kirkpatrick J and Mirjalili SA J Ped Urol 12: 275-80. 2016

- Unable to ascend. “Held back by inferior mesenteric artery”, though immediately inferior in 40%
- Obstruction common due to malrotation, ureter coursing over parenchyma, highly variable vascular structure
- Division of isthmus rarely needed for de-obstruction

Ureteropelvic Junction Obstruction

- Intrinsic Obstruction (narrow lumen)
 - Aperistaltic segment arises from premature arrest of ureteral differentiation near UPJ
 - Persistence of fetal folds in the ureter
 - Extreme lack of smooth muscle differentiation in a region that normally has less smooth muscle
- Extrinsic Obstruction
 - Crossing vessels
 - Adhesions/fibrosis from infection or instrumentation
- Secondary Obstruction
 - Compensatory hydronephrosis can exacerbate original cause
 - Association with high grade reflux but not common enough to establish causality

Diagnosis of UPJ obstruction

- Historically found after infection, pain, stones or hematuria
- Currently, most are diagnosed on prenatal US
- Management less certain in asymptomatic cases (the majority)

Evaluation of UPJ obstruction

- Diagnosis is made as part of evaluation for prenatally diagnosed hydronephrosis
- Main question “Is there significant enough obstruction to cause pathological changes?”
- Clinical signs of pain, stone formation, bleeding and infection all favor repair

Defining Obstruction

- Typically motivated by clinical signs, worsening hydronephrosis on serial US, or initial severe presentation (gr3-4)
- Nuclear renal scan
- Resistive index on Doppler US
- Whitaker test

Ultrasound

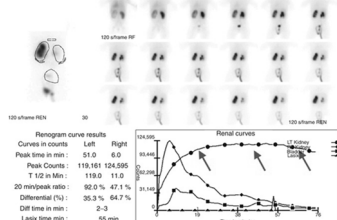
- Resistive index= (peak systolic velocity-end diastolic velocity)/peak systolic velocity
- RI > 0.70 suggests obstruction
- Initial studies encouraging but not supported in later investigations
- Common for babies (<1 yr) to have RI >0.70 (up to age 4)
- Not frequently used if other modalities available

Nuclear Renal Scan

- Most common study using ^{99m}Tc -MAG3 with Lasix diuretic challenge
- Child must be at least 2-3 months of age
- Bladder catheter for VUR, children who cannot voluntarily void, bladder pathology or pelvic kidney
- Standardize timing of Lasix. F+15 mins
- RRF < 40% relative indication for surgery. Obstruction can delay uptake-appears worse
- Elicitation of Dietl's crisis should be evaluated

MAG3 with Lasix Renal Scan

- Unobstructed T1/2 < 10 minutes; Equivocal 10-20 minutes; Obstructed > 20 minutes



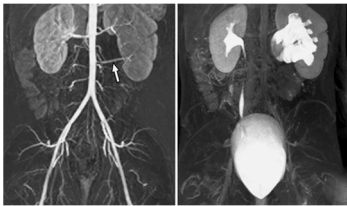
Schlomer B.J., Cohen R.A., Baskin L.S. (2014) Renal Imaging: Congenital Anomalies of the Kidney and Urinary Tract. In: Palmer L., Palmer J. (eds) Pediatric and Adolescent Urologic Imaging. Springer, New York, NY

Whitaker Test

- Useful when massive dilation or poor renal function confounds nuclear scan
- Percutaneous administration of contrast at 10mL/min while monitoring of infusion and intravesical pressure
- Normal 0-15cm H₂O, Equivocal 15-22cm H₂O, Obstructed >22 cm H₂O

Other modalities

- CT: rarely used, very high radiation
- MR Urogram: Emerging technology without ionizing radiation. Can combine functional with anatomic imaging. Sedation requirement in younger patients



Parikh KR et al. Ped Radiol
12:1788-95. 2015

Surgical Repair of UPJ obstruction

- Timing controversial. Earlier repair affords greater recovery potential.
- Dismembered pyeloplasty versus Y-V plasty. Latter may be useful for high insertions.
- Open versus laparoscopic
- Endoscopic approach
- Stenting or not

Open versus Laparoscopy

- Significant pain/recovery advantage for laparoscopy in older children
- Dorsal lumbotomy or small subcostal incision with infants and younger children.
- Lap retroperitoneal approach less risky but technically more challenging

Endopyelotomy

- Retrograde or antegrade with balloon, Accusize, or laser.
- Significantly lower success rate compared to open/lap repair of primary UPJO (ca. 60 vs 90% success rate)
- Possible bleeding with crossing vessel
- Stenting for 6 weeks post op
- May be useful after failed primary repair but most of those patients undergo repeat repair

Post-op Stenting

- 4-6 weeks
- Double j stents common but require second anesthesia in children. Induces VUR-many leave Foley 1-2 days post op.
- Ureteropyelostomy tube can be brought out of abdominal wall. Removed without anesthesia.
- Non-stenting. Greater risk of leakage and acute obstruction from inflammation/edema or clots.

Pediatric Renal Cystic Disease

- Genetic: autosomal recessive polycystic disease, autosomal dominant polycystic kidney disease, glomerulocystic kidney disease, medullary cystic dysplasia
- Non-genetic: renal dysplasia, multicystic dysplastic kidney, obstructive cystic dysplasia, nongenetic nondysplastic cysts, simple cyst, multilocular cyst, medullary sponge kidney

Evaluation of Pediatric Renal Cysts

- Family history
- Physical exam: associated anomalies, palpable kidneys/cysts
- Ultrasonography
 - Size, number, complexity and location of cysts
 - Echogenicity of parenchyma compared to liver or spleen
 - Corticomedullary differentiation

Autosomal recessive polycystic kidney disease

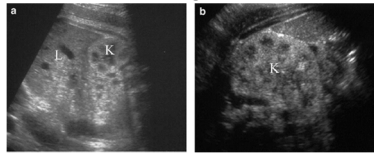
- Often fatal in infancy due to renal failure and hepatic fibrosis
- Cystic dilation of tubules in the medulla, hepatic fibrosis
- Large hyperechoic kidneys, no corticomedullary differentiation



Avni FE et al Ped Radiol 35(5): 405-14. 2006

Autosomal Dominant Polycystic Kidney Disease

- Positive family history about 50%
- Cysts may not develop until adulthood
- US often shows moderately enlarged kidneys with hyperechoic cortex, hypoechoic medulla
- Cysts only treated (excision, marsupialization) if symptomatic-pain, infection, bleeding, obstruction

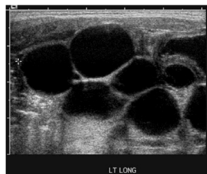


Avni FE et al Ped Radiol 35(5): 405-14. 2006

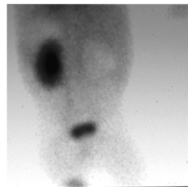
Multicystic Dysplastic Kidney

- Thought to result from complete obstruction early in development or aberrant epithelial/mesenchymal signaling
- Ultrasound shows multiple non-connecting cysts of variable size, variable amount of echogenic stroma, no normal cortex or medulla, irregular contour, no collecting system
- Nuclear scan shows no activity- useful if needed to rule out severe obstructive hydronephrosis or cystic Wilm's tumor

Imaging of MCDK



Raviv-Zilka L et al Urol Sci 27(3): 158-60. 2016



Nepple KG and Cooper CS in Pediatric Urology for the Primary Care Physician, Rabinowitz et al (eds.) Current Clinical Urology. Springer. New York. 2014

Associated Anomalies

- Overall 5-48%
 - Contralateral VUR
 - Contralateral UPJ obstruction
 - Contralateral UVJ obstruction
 - Less likely- ureterocele, horseshoe kidney

Natural course

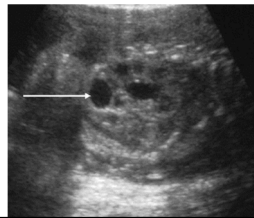
- Over half involute by age 10
- Compensatory hypertrophy found in over 90% by adolescence
- Hypertension develops at similar rates to general population. Nephrectomy cures about half.
- Malignancy extremely rare with proper imaging

Management of MCDK

- Confirmatory nuclear scan only needed if ultrasound ambiguous
- VCUG if infections present or if contralateral kidney is abnormal/hydronephrotic
- Serial US imaging controversial. Common to follow initial postnatal US at one year to evaluate contralateral kidney
- Nephrectomy rare. Indications would be for intractable HTN, enlargement, infection

Simple Renal Cysts

- Most are asymptomatic, incidental findings with no clinical relevance
- No advanced imaging unless unclear



Avni FE et al Ped Radiol 35(5): 405-14. 2006

Management of Simple Cysts

- Annual US to assess for enlargement
- Indications for Surgery
 - Pain due to enlargement (usually >10cm)
 - Infection
 - Obstruction
- Surgical Strategies
 - Open/laparoscopic excision
 - Open/laparoscopic marsupialization
 - Aspiration and sclerosis- high rates of recurrence

Pediatric Nephrolithiasis

- Not as common in children but incidence rising over past decades. Environmental and dietary causes suspected.
- More common in children with metabolic, genetic or anatomic abnormalities

Evaluation of New Stone Patients

- History and Physical
- Diet: Low fluid intake, high sodium, excessive protein, ketogenic diets, all increase risk
- Medications: vit D, Ca, Vit C, diuretics, steroids, uricosuric drugs and antibiotics (indinavir, ceftriaxone)
- Family history: may be due to genetics or shared environment/diet

Co-morbid Conditions

- Urinary tract obstruction
- Vesicoureteral reflux
- Immobilization
- Neurogenic bladder
- Inflammatory bowel disease
- Short gut syndrome
- Cystic fibrosis
- Seizure disorders

Metabolic Abnormalities (Initial evaluation)

- List is extensive. Unless provider specifically trained, referral to pediatric nephrology.
- Most common include hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, cystinuria
- Two 24 hour urine collections recommended due to variability. Need to adjust expected range based on age/size.
- Comprehensive metabolic panel. Must collect at same time of urine collection.

Pediatric Stone Imaging

- CT scan gold standard for adults, very high radiation.
- Ultrasound first and often only imaging study needed for children.
- Reserve CT where there is clinical suspicion and a negative US AND the result will change management.
- Abdominal X ray helpful after US to determine potential for ESWL

Acute Management

- Analgesia: Acetaminophen, NSAIDs (Toradol), narcotics
- Indications for intervention
 - Infection
 - Impassable stone (>5mm)
 - Intractable pain
 - Failed trial of passage and patient desire
- Ureteral stenting versus Nephrostomy tube

Treatment of Stones

- Medical expulsive therapy: Controversial as in adults. Tamsulosin 0.4mg qd with 4-6 week trial.
- Ureterscopy: Stenting 4-6 weeks prior may be necessary for access, decrease trauma.
- Percutaneous nephrolithotomy: Avoids ureteral trauma, new “mini-perc” equipment
- Extracorporeal shock wave lithotripsy: Effective in children, does require passage of fragments

Prevention of Pediatric Stones

Metabolic Abnormality	Conservative Management	Medication
Hypercalciuria	Increase fluid intake Limit dietary sodium intake Consume RDA of dietary calcium Avoid excessive protein intake Normalize vitamin D status	Potassium citrate Thiazides
Hypocitraturia	Encourage intake of dietary citrate Increase intake of fruits and vegetables Avoid excessive protein intake	Potassium citrate Bicarbonate
Hyperoxaluria	Increase fluid intake Reduce dietary oxalate Consume RDA of dietary calcium Treat fat malabsorption, if present Probiotics	Potassium citrate Pyridoxine Neutral phosphate Magnesium
Hyperuricosuria	Increase fluid intake Decrease intake of purine-rich foods Avoid excessive protein intake	Potassium citrate Bicarbonate Allopurinol
Cystinuria	Increase fluid intake Limit dietary sodium intake	Tiopronin Penicillamine Captopril

Hernandez JD, Ellison JS and Lendvay TS. JAMA Pediatrics 169(10): 964-70. 2015

Fluid Recommendations

- Increase the Dilution, Decrease the Pollution
- Fluid intake should be minimum of 1.5-2L/m²/day which translates to:

AGE	Minimum (mL)/day
Infant	750
<5 years	1000
5-10 years	1500
>10 years	2000

END OF CHAPTER

Common Pediatric Urology Conditions:

Congenital Disorders, Bladder

Hillary L. Copp, MD, MS
Associate Professor, Pediatric Urology
University of California, San Francisco



Congenital Disorders of the Bladder

- I have no disclosures

Congenital Disorders of the Bladder

- Neurogenic bladder
- Lower urinary tract obstruction
- Prune Belly Syndrome
- Exstrophy-epispadias complex
- Urachal abnormalities
- Bladder diverticulum
- Bladder masses

Congenital Disorders of the Bladder

- Neurogenic bladder
 - Spina bifida: 29.01/100,000
- Lower urinary tract obstruction
 - Posterior urethral valves: 11.02/100,000
- Prune Belly Syndrome
 - 3.28/100,000
- Exstrophy-epispadias complex
 - Bladder exstrophy: 1.63/100,000

Lloyd 2013

Congenital Disorders of the Bladder

- **Neurogenic bladder**
 - Spina bifida: 29.01/100,000
- Lower urinary tract obstruction
 - Posterior urethral valves: 11.02/100,000
- Prune Belly Syndrome
 - 3.28/100,000
- Exstrophy-epispadias complex
 - Bladder exstrophy: 1.63/100,000

Lloyd 2013

Neurogenic Bladder

- Spina bifida
- Tethered cord
- Sacral agenesis
- Cloacal anomaly
- Anorectal malformation
- Cerebral palsy

Neurogenic Bladder

- Spina bifida most common cause
 - Birth prevalence: 29.01/100,000 children
- Myelomeningocele accounts for >90% of all open spinal dysraphic states

Spina Bifida

- Majority of defects occur at lumbar vertebrae
 - Level of vertebral defect does not correlate with neurologic lesion
 - Neurologic sequelae depend on which neural elements evert into the meningocele sac
- Neurologic lesion is a dynamic condition that can change with linear growth

Neurogenic Bladder

- Normal lower urinary tract function
 - Low pressure urine storage
 - Periodic voluntary emptying
- Neurogenic bladder
 - Bladder dysfunction caused by neurologic malformation or damage

Neurogenic Bladder

- GU complications major source of morbidity
 - Incontinence, recurrent UTI, chronic renal insufficiency, and end-stage renal disease
- Optimal urologic care not known
 - Routh 2016: CDC-sponsored, prospective protocol for management of children with spina bifida
 - 5-yr outcomes assessment: UTIs, renal function, renal scarring and clinical process improvements

Neurogenic Bladder Goals

- Preservation of low pressure storage and efficient emptying
- Prevention of upper tract changes and maintenance of normal renal function

Evaluation: Ultrasound

- A window into bladder behavior to detect lower tract changes prior to upper tract damage
- Not good for detection of renal scarring
 - Veenboer 2015: 10% with scars on ultrasound, 46% with scars on DMSA scan

Evaluation: Urodynamics

- Assess intravesical pressures, capacity and detrusor leak point pressure (DLPP)/end fill pressure (EFP)
- Recommended urodynamics schedule variable
 - CDC protocol
 - Newborn period
 - Yearly during 1st 3 years of life
 - Repeat each year if VUR present on last UDS until age 5
 - Urodynamics if clinical change: new hydronephrosis, new incontinence, UTI

Evaluation: Kidney Function

- Serum creatinine between 1-3 months of age and then yearly thereafter
 - Cordeiro 2008: Serum creatinine unreliable in spina bifida patients from decreased muscle mass (muscle wasting) and short stature (scoliosis)
- Renal scan at 1-3 months of age for baseline split renal function

Management: Clean intermittent catheterization (CIC)

- Before CIC: renal failure most common cause of death at all ages in spina bifida patients
 - Sawin 2015: 74% of patients in National Spina Bifida Registry use CIC
- Indications for, timing of, and schedule of CIC varies in newborn period
 - Joseph 1989: Easier acceptance of CIC by parents and children as they grow older if initiated earlier

Management: Medications

- Anticholinergic medications should be initiated in hostile bladders
 - DLPP/EFP > 40cm H₂O
 - Neurogenic detrusor overactivity
 - Detrusor sphincter dyssynergia
- 0.2 mg/kg oxybutynin orally tid

Management: Medications

- Prophylactic antibiotics
 - Antibiotic use in vesicoureteral reflux related to neurogenic bladder is controversial
 - CDC protocol: used if grade V reflux or lower grade reflux + hostile bladder

Surgical Management: Intradetrusor Onabotulinumtoxin A

- Intradetrusor Onabotulinumtoxin A = Botox
- Dosing: 10-12 units/kg, max dose 300 units
 - Used for a variety of conditions
 - Cumulative dose: ≤360 units in a 3 month interval
 - Adverse effect from risk of toxin spread
 - Asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysarthria, breathing difficulty, paralysis of respiratory muscles and intubation

Surgical Management: Botox

- Khan 2016
 - 50%: no improvement in incontinence
 - If response, mean duration: 4.6 months
- Kask 2014, Tiryaki 2015
 - Poorest response if severely impaired compliance or fibrotic bladder
 - Significant increase in capacity and compliance when main indication is detrusor overactivity

Surgical Management: Botox

- Disadvantages of Botox
 - Requires regular injections with recurrent anesthesia exposure
 - Chohan 2015: loss of efficacy over time

Surgical management: Surgical Reconstruction

- If fail medical and intravesical treatment options, surgical reconstruction performed
 - Bladder failure with intact sphincter and ability to catheterize per urethra: bladder augmentation
 - Bladder augmentation with non intact sphincter: bladder augmentation with outlet procedure and continent catheterizable channel

Congenital Disorders of the Bladder

- Neurogenic bladder
 - Spina bifida: 29.01/100,000
- **Lower urinary tract obstruction**
 - **Posterior urethral valves: 11.02/100,000**
- Prune Belly Syndrome
 - 3.28/100,000
- Exstrophy-epispadias complex
 - Bladder exstrophy: 1.63/100,000

Lloyd 2013

Lower Urinary Tract Obstruction

- Intrinsic
 - Posterior urethral valves
 - Urethral atresia
 - Anterior urethral valves
 - Congenital megalourethra
- Extrinsic
 - Outlet compression from pelvic mass

Posterior Urethral Valves

- Obstructing membrane in posterior urethra
- Most common cause of lower urinary tract obstruction in males
- Birth prevalence: 11.02/100,000
- Accounts for 17% of renal failure in kids

Posterior Urethral Valves

- Obstruction develops early in gestation
 - Urethra develops at 14 weeks of gestation
 - Valves present prior to this time
 - Obstruction begins with urine production
- Bladder and upper urinary tract are exposed to elevated pressure during development
 - Affects bladder development and function
 - Causes renal injury

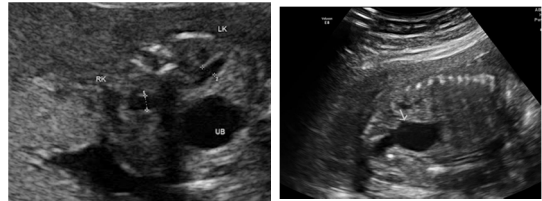
Posterior Urethral Valves

- Usually detected prenatally
 - Hydronephrosis
 - Distended, thick-walled bladder
 - Oligohydramnios
 - "Keyhole" sign

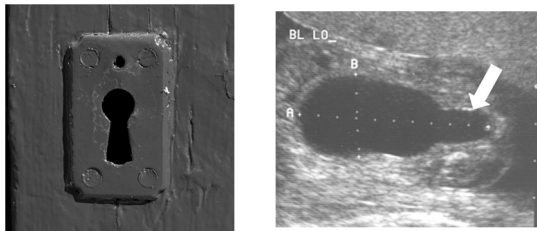
Presentation

- Cases not detected prenatally
 - If present after birth may see poor urinary stream, UTI, and/or failure to thrive
- Older children may present secondary to diurnal enuresis, UTI, severe LUTS (dribbling, retention, hematuria)

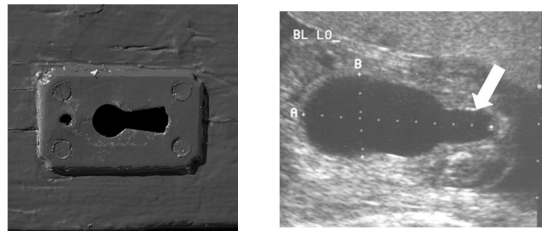
Fetal Ultrasound Findings



Keyhole appearance



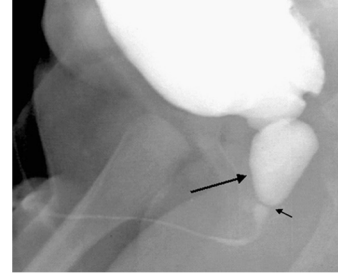
Keyhole appearance



Postnatal Management

- Bedside management
 - Catheter placement
 - Labs: monitor electrolytes and renal function
 - Antibiotics
- Imaging
 - RBUS
 - VCUG

VCUG



Surgical Intervention

- Circumcision + ...
 - Bader 2013: 83% reduction in UTI
- Valve ablation
- Cutaneous vesicostomy
 - Indications for vesicostomy
 - <2000g infant
 - Urethra can't accommodate cystoscope

Vesicoureteral Reflux

- 50% will have VUR at diagnosis
- After ablation VUR resolves in up to 1/3
 - May take months to several years
 - More likely to resolve if bilateral
 - Less likely to resolve if kidney function is poor

Smith 1996, Hassan 2003

Vesicoureteral Reflux

- Persistent high-grade VUR usually from persistent bladder dysfunction
 - High bladder storage pressures and poor drainage
- High risk for complications due thick-walled bladder and voiding dysfunction
 - UDS, check for persistent valve remnants
 - Rarely reimplant: only if persistent infection AND bladder function adequately managed

Kim 1997

Hydronephrosis

- Most have severe hydronephrosis at diagnosis
 - Not always associated with VUR
 - Urine concentrating defect and polyuria
- ~50% of nonrefluxing hydronephrosis resolves with valve ablation
- Persistent hydronephrosis common

Tietjen 1997 Glassberg 1982

Valve Bladder Syndrome

Mitchell 1982

- Despite valve ablation intrinsic bladder dysfunction leads to deterioration of the upper tracts and incontinence

Pathophysiology

- Compensated phase
 - Bladder wall hypertrophy develops
 - Bladder generates high voiding pressure
 - Bladder usually able to empty

Pathophysiology

- Decompensated phase
 - Further hypertrophy
 - Detrusor begins to decompensate
 - Postvoid residual increases
 - Storage pressure rises

Pathophysiology

- Elevated intravesical storage pressures transmit to upper tracts
- Elevated renal pelvic pressures overtime can affect renal morphology and function
 - Decreased renal concentrating ability
 - Decrease in GFR
- Overtime polyuria and compensatory polydipsia

Valve Bladder Variability

- Hyperreflexic (uninhibited contractions)
 - May respond to anticholinergic therapy
- Small noncompliant
 - May respond to anticholinergic therapy
 - May need CIC
 - May need augmentation
- Myogenic failure
 - Need CIC

Breaking the cycle...

- Start with timed voiding, double voiding
- Monitor closely
- Management guided by ultrasound and urodynamics
- Koff 2002
 - This is not a permanent state...It is an induced condition from polyuria, impaired bladder sensation, and PVR

Breaking the cycle...

- CIC plus overnight catheter drainage
 - Reduces the strain of high output on urinary tract
 - Provides prolonged period of rest
- Results: improved GFR, improved bladder compliance and capacity, decreased hydronephrosis

Koff 2002, Holmdahl 2003

Incontinence

- Up to 80% with delayed day and night continence at 5 years, 50% at 12 years, improves by 20's
- Causes: poor bladder sensation, poor compliance, detrusor instability, and polyuria
- Treatment varies: timed/double voiding, anticholinergics, CIC...augmentation

Churchill 1990, Smith 1996

Prognosis

- Predictors of poor renal function
 - Ultrasound
 - dysplasia estimation, severe hydronephrosis
 - Creatinine at 1 year (1 ng/dL)
 - VUR
 - Bilateral VUR
 - Recurrent UTI

ESRD

- Up to 50% with PUV will have ESRD in lifetime
 - More modern studies up to about 30% with ESRD
 - Can happen early or later (in twenties)
- UDS evaluation prior to transplant

Tanaka 2011, Sarhan 2011

Congenital Disorders of the Bladder

- Neurogenic bladder
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- **Prune Belly Syndrome**
 - 3.28/100,000
- Exstrophy-epispadias complex
 - Bladder exstrophy: 1.63/100,000

Lloyd 2013

Prune Belly Syndrome

- The Triad
 - Deficiency of abdominal wall musculature
 - Bilateral cryptorchidism
 - Dilated urinary tract



Prune Belly Syndrome

- Birth prevalence: 3.8/100,000
- Unknown etiology
- 5% occurs in females: "pseudoprunes"
 - Abdominal wall abnormality
 - Dilated urinary tract
 - Often have omphalocele, lower urinary tract obstruction
- Up to 40% with anorectoabnormalities

Druschel 1995, Reinberg 1991,
Routh 2010

Prune Belly Syndrome

- Smith 2001: morbid condition
 - 20% still born
 - 30% die during initial hospitalization
 - 40% born prematurely
 - 50% significant urinary pathology during lifetime
 - 70% with renal insufficiency
 - 50% with respiratory issues

Woodard's Classification

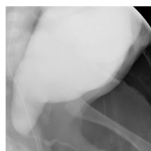
- Category I: most severe
 - Pulmonary hypoplasia and severe renal dysplasia
 - Usually do not survive beyond 1st few days of life
- Category II
 - No pulmonary hypoplasia
 - Significant urinary tract involvement with renal dysplasia
 - Typical external features

Woodard's Classification

- Category III
 - External features mild or incomplete
 - Uropathy less severe, often with stable renal
 - Stable pulmonary function

Genitourinary Manifestations

- Bladder
 - Thick-walled, enlarged
 - Usually not trabeculated
 - Wide bladder neck
- Prostate
 - Hypoplastic
- Posterior urethra
 - Dilated, elongated
 - Tapers at membranous portion



Genitourinary Manifestations

- Hydronephrosis
 - Often ureteral dilation > hydronephrosis
- Elongated, tortuous, and dilated ureters
 - Distal 1/3 worse than proximal ureter
 - Obstruction not common
 - 85% with VUR



Genitourinary Manifestations

- Testes
 - Usually intra-abdominal
- Accessory male organs
 - Non union of epididymis
- Decreased spermatogonia
- Thickened vasa
- Leydig cell hyperplasia
- Abnormal seminal vesicles (absent, thick, dilated, etc)

Extragenitourinary Manifestations

- Abdominal wall muscular deficiency
 - Walking delayed
 - Pulmonary infections and constipation
- Orthopedic (60%)
 - Hip dislocation
 - Scoliosis
 - Limb deformities from oligohydramnios
- Gastrointestinal (30%)
 - Malrotation, volvulus
- Pulmonary (55%)
 - Chronic bronchitis
 - Respiratory insufficiency after URI or anesthesia
- Cardiac (10%)
 - PDA, ASD, VSD

Evaluation and Management

- Prenatally: difficult to distinguish from other causes of hydronephrosis such PUVs
- Postnatally: Diagnosis by appearance
 - Creatinine
 - Start prophylaxis
 - Avoid urinary tract instrumentation
 - Orchiopexy b/t 6-12 months
 - +/- urinary tract and abdominal reconstruction

Congenital Disorders of the Bladder

- Neurogenic bladder
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- Prune Belly Syndrome
 - 3.28/100,000
- **Exstrophy-epispadias complex**
 - **Bladder exstrophy: 1.63/100,000**

Lloyd 2013

Exstrophy-epispadias Complex

- Bladder exstrophy: bladder is an open plate on the low abdominal wall with epispadias
 - 1.63/ 100,000
- Epispadias: urethra is a partial or complete open plate on the dorsal aspect of phallus
 - 11.58/100,000

Bladder Exstrophy

MALE



FEMALE



Exstrophy-epispadias Complex

- Cloacal exstrophy:
1/200,000 – 1/400,000
- Bladder exstrophy
- Hindgut exstrophy
 - ileocecal junction of bowel is an an open plate
 - ileal intussusception
 - exposed appendices
- Penis/clitoris split into 2 halves with epispadias



Associated Findings

- Diastasis pubis due to outward rotation of innominate bones
- Umbilical hernias uniform
- Females: absent mons pubis
- Males: short, broad penis
 - Silver 1997: short total corporal length due to foreshortened anterior corporal segment

Common Occurrences

- VUR almost uniformly after closure of exstrophy due to laterally placed ureters
- Inguinal hernias common
 - Husmann 1990: repair recommended at time of primary repair to prevent incarceration

Other Anomalies

- Classic exstrophy and epispadias have a low incidence of other anomalies
- Cloacal exstrophy other anomalies frequent
 - Genitalia: UDT, uterine and vaginal anomalies
 - Skeletal: club foot, hip dislocation
 - neurologic issues: 50-100% have spinal cord involvement

Diagnosis

- Prenatal findings
 - Absent bladder
 - Lower abdominal protrusion
 - Anterior scrotum with small phallus
 - Low set umbilical cord
 - Abnormal iliac crest widening
- Most often diagnosed at time of delivery

Newborn Management

- Tie off umbilical cord with suture to avoid trauma to bladder plate
- Plastic wrap on bladder plate, replace daily
- Saline irrigate bladder plate each diaper change

Evaluation and Management

- Baseline RBUS for upper tract evaluation
- KUB to assess level of diastasis
- Spinal ultrasound if sacral abnormality

Evaluation and Management

- Orthopedic consultation to plan for osteotomies if needed
 - >72 hours old, wide diastasis
- Allows for pubic symphysis apposition, diminishes tension on closure, optimizes anatomic position of the bladder within the pelvis

Surgical Repair

- Staged reconstruction
 - Bladder, posterior urethra and abdominal closure
 - Epispadias repair between 6-12 months of age
 - Delayed bladder neck repair at 4-5 years of age
- Complete primary repair
 - Correct abnormalities in one setting
 - May avoid need for bladder neck reconstruction

Congenital Disorders of the Bladder

- Overall incidence is low
- Anomalies may be significant with severe consequences
- Early detection and management are critical to prevent further urinary tract deterioration

Congenital Disorders of the Bladder

Thank you!

Pediatric Urologic Trauma

August 7th, 2018

Michael P. Kurtz, MD, MPH
Associate in Urology, Boston Children's Hospital
Assistant Professor of Surgery, Harvard Medical School



Boston Children's Hospital
Until every child is well



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

I have no disclosures relevant
to the content of this lecture



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Outline

- Renal trauma: staging, management
 - The solitary kidney
- Bladder trauma
 - Specific attention to the bladder neck
- Lower GU trauma
 - Penopubic
 - Scrotal



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Renal Trauma in Children is Common

- Reasons unknown
 - Less peri-renal fat?
 - More flexible rib cage?
 - Kids more exposed to bicycle handlebar injuries?
- Odds of renal trauma after a motor vehicle collision are about 50% higher in children than adults, adjusting for overall injury severity

Blunt Abdominal Trauma from Motor Vehicle
Accidents: Kidney Injuries in Children versus
Adults, in a National Sample, J Urol 2016



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When to work up a child for renal injury?

- The "Textbook" answer
 - Difficult to rely on pediatric hematuria
 - It's often way too late to rely on hypotension
- Therefore – rely on *mechanism*



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Until every child is well



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Dr. Husmann's Campbell's Chapter

BOX 154-1 Indications for Radiographic Assessment of Pediatric Patient for Possible Genitourinary Injury

All penetrating abdominal/pelvic traumas
or

A history of blunt abdominal trauma that meets one of the four
following criteria:

1. A significant deceleration or high-velocity accident, fall from greater than 10 feet, or strike to the abdomen or flank with a foreign object (e.g., football helmet, baseball bat, hockey stick)
2. Significant trauma that has resulted in injuries to the thoracic contents and/or intra-abdominal organs, and/or orthopedic fractures of the ribs, spine, pelvis, or femur
3. Gross hematuria
4. Microscopic hematuria (>50 RBC/HPF) associated with shock (systolic blood pressure <90 mm Hg)

HPF, high-power field; RBC, red blood cells.



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A relevant pearl

- Blood volume is *approximately* 70-80 cc/kg (i.e. 7-8% of bodyweight) for children
 - Even higher percentage in infants and neonates
 - For adolescents, use adult formula (7%)
 - Volume is about 0.5% higher in males
 - Adjust down about 1% (6%) if obese
- There are only 5 places you can lose two units of red cells, or equivalent volume in children

What about FAST?

- "Focused Assessment with Sonography in Trauma"
- Initially targeted at hemoperitoneum in unstable patients, and has been expanded to include point-of-care ultrasound in trauma
 - Reardon, acep.org
- Plenty of reports of diagnoses of renal hematoma in children with POC ultrasound
 - Pershad & Gilmore, Ped Emerg Care 2000

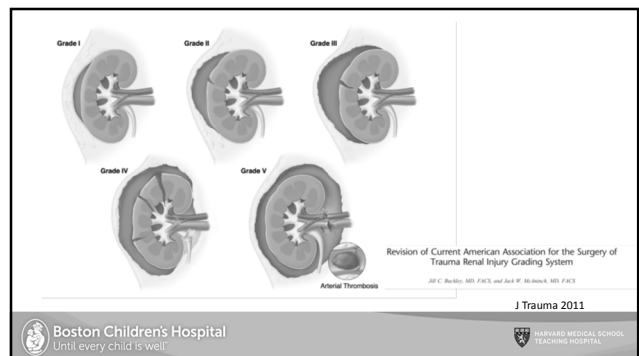
Stage the injury

- CT remains the gold standard
- Perform with IV contrast and delays
 - Delays *not* sufficient to stage bladder injuries

Revision of Current American Association for the Surgery of Trauma Renal Injury Grading System

J Trauma 2011

Grade	Injury Definition
I	Subcapsular hematoma and/or contusion No injury
II	Pararenal hematoma No injury
III	Pararenal hematoma No injury
IV	Pararenal hematoma No injury
V	Pararenal hematoma No injury



My simple AAST revised staging mnemonic

Grade	Injury Definition
I	Subcapsular hematoma and/or contusion No injury
II	Pararenal hematoma No injury
III	Pararenal hematoma No injury
IV	Pararenal hematoma No injury
V	Pararenal hematoma No injury

- Grade 1 = A bruise
- Grade 2 = <1cm laceration, small hematoma
- Grade 3 = >1cm laceration, any hematoma w/in Gerota's [...]
- Grade 5 = avulsed or thrombosed hilum
- Grade 4 = Everything else*
- *Any urinary extravasation, segmental vessel injury, UPJ disruption, presumably a hematoma through Gerota's
- ** Note "devitalized" and "shattered" are not in staging

Classic Predicators of Intervention

- Lateral extravasation without ureteral visualization
 - Suggests ureteral injury/distruption
- Medial contrast extravasation
 - Hilar, or pelvic injury
- Peripheral hematoma larger than an inch (2.5cm)

(Nuss et al, 2009; Charbit et al, 2011)

Post-Injury Follow-up Imaging

- For all serious injury (grade 2+) we obtain a blood pressure, UA and ultrasound at 6 weeks
 - Then DMSA only if question of viability or renovascular HTN
 - Some reserve imaging only for grade IV and higher or if fragments are devitalized
 - Concern is for long term renovascular complication
- This is *distinct* from follow-up evaluation for delayed hemorrhage

Classic Hydronephrosis + Trauma Questions

- Preexisting hydronephrosis increases the odds of renal trauma
- Mostly, this is parenchymal rather than a UPJ disruption
- When UPJ disruption is suspected (medial contrast extravasation, no contrast in ureter, minor renal cortical injury), retrograde pyelography can confirm this
- Some authors prefer immediate repair with liberal drain placement; I prefer a nephrostomy and interval repair

The Solitary Kidney and Injury Prevention

- What sports are safe?
- Are any sports safe?
- What precautions are necessary?

My favorite nephrology line regarding participation in sports with one kidney

"Well, you only have one head!"

The National Football League

- In the US, "can my child play football?" knowing that they have a single kidney is a common question
- The fear is that a solitary kidney is a form of CKD, and contralateral injury can accelerate this

Nice Review: Psooy 2006, CUA

- "Evidence – Level 4: Although protective padding is available, there is no evidence to demonstrate that they prevent renal injuries."
- "Those activities most associated with high-grade renal trauma (bicycling, sledding, downhill skiing, snowboarding and equestrian) have more than a fivefold relative risk of head injury compared to renal injury."

More CUA guidelines

- “The use of all-terrain vehicles (ATVs) by children is associated with high-grade kidney trauma. However, unlike other recreational activities mentioned in this guideline, there are formal recommendations against the operation of ATVs by all children less than 16 years of age, regardless of kidney number. “

The American Academy of Pediatrics

- Recommends a “qualified yes” for participation in contact or collision sports for young athletes with a single kidney
- “Athlete needs individual assessment for contact, collision, and limited-contact sports. Protective equipment may reduce risk of injury to the remaining kidney sufficiently to allow participation in most sports, providing such equipment remains in place during activity.”

<https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/Young-Athletes-Unlikely-to-Injure-Kidney-Playing-Contact-Sports.aspx>

Medical Conditions Affecting Sports Participation
Stephen G. Rice and the Council on Sports Medicine and Fitness

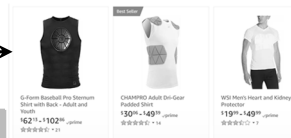
Two families of protectors

- Rigid, typically made in a brace shop



- “Amazon funkiness”

- Nonmedical
- Rational placement of pads



What I tell families

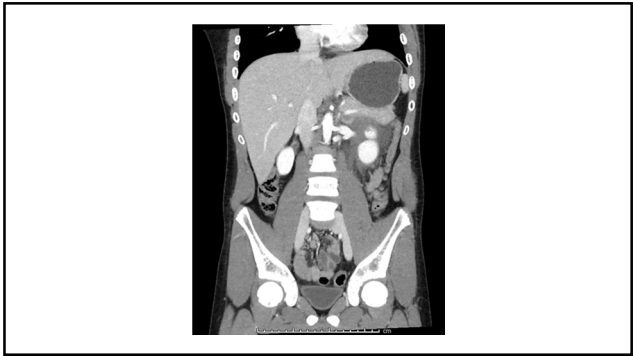
- Protecting your good kidney from factors inside and outside of your body is important (segue into nephrology)
- Wearing seatbelts and avoiding ATVs are most important, followed by limiting exposure to high-velocity sports (ski racing, horseback riding). Be careful on bikes, sleds.
- For standard team sports, it's safe. In this history of the NFL, nobody has ever lost a kidney. Wearing kidney protectors won't hurt, but benefit remains to be proven

Your mileage may vary

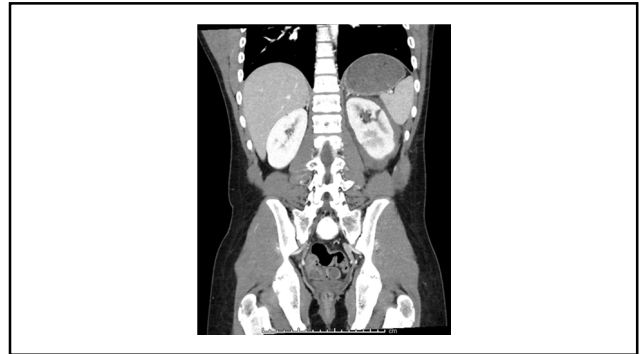
- I refer children with solitary kidneys to nephrology
- The longer term relationship, with precise monitoring of blood pressure (quite hard in infants and young children!) and microalbuminuria, is more important than what I offer in my clinic
- Nephrologists may have a different perspective on CKD

Renal Trauma Case

- 11-year-old male, healthy
- Fall during motocross race
- Rider off jump to ground at 40-50 MPH estimated
- Full protective equipment, no LOC
- One episode of gross hematuria
- Hemodynamically normal, no other injuries on exam





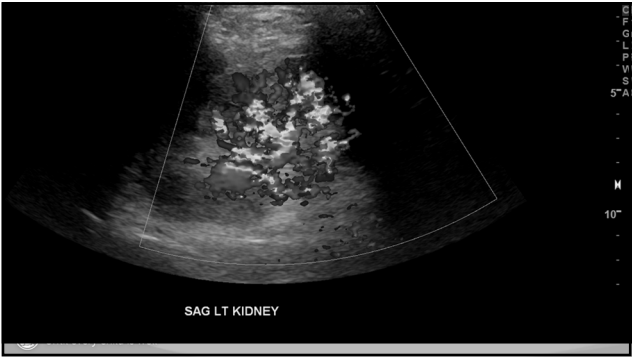
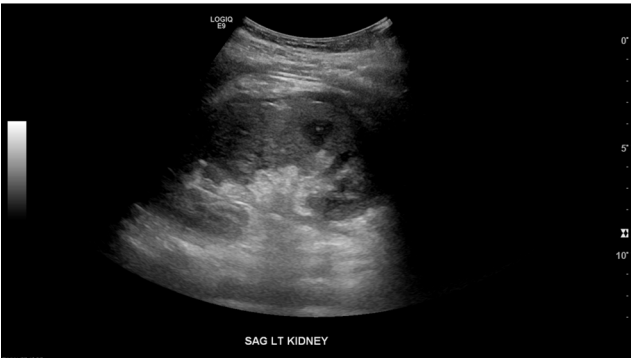
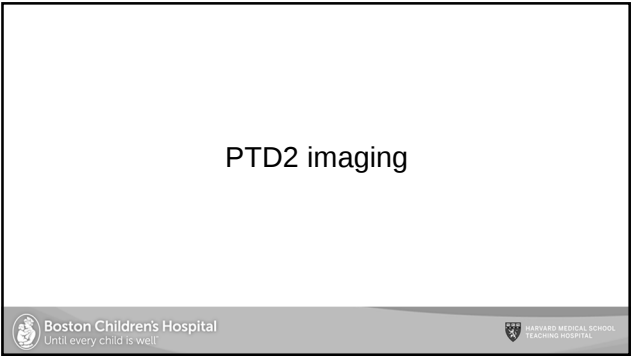


CT obtained before transfer

- 1.8 cm laceration into pelvis, separate >2cm laceration through the lower pole
- No extravasation (portal venous phase)
- No delayed images
- High attenuation hematoma

Next steps

- Hemodynamically normal
- CT with delays?
- IVP / retrograde?
- Ultrasound?



6 weeks post trauma, normal blood pressure and ...

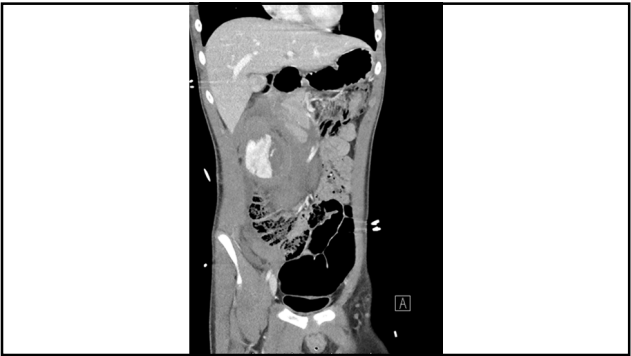
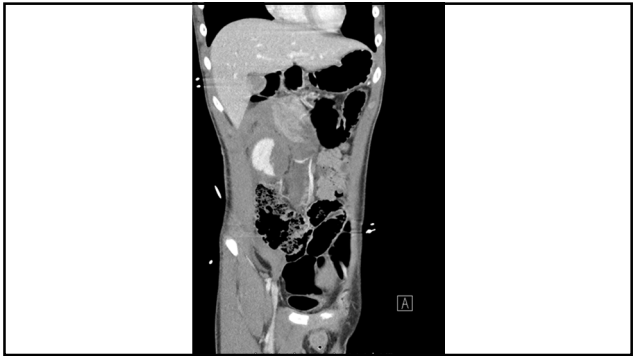


2nd Case, Renal Trauma

- 13yM, previously healthy
- Belted front-seat passenger, driver veered off road at 50 MPH
- Rollover, father rescued son from rescued from inverted vehicle, transferred to local hospital and MedFlight to Boston PTD1
- Trauma workup reveals pulmonary contusion, no fractures



Initial CT scan

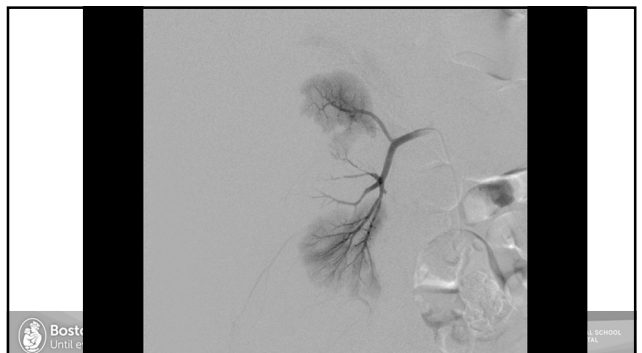


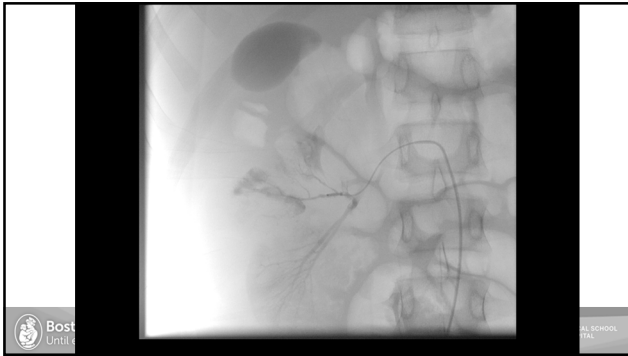




Update

- Post-trauma day 1, Hct is 17 from 28, and he has required 6 units of red cells
- Intermittently hypotensive





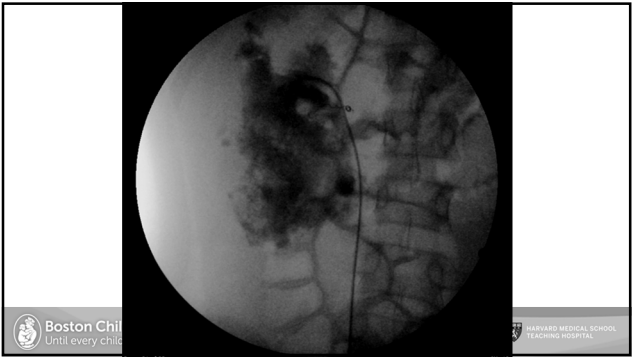
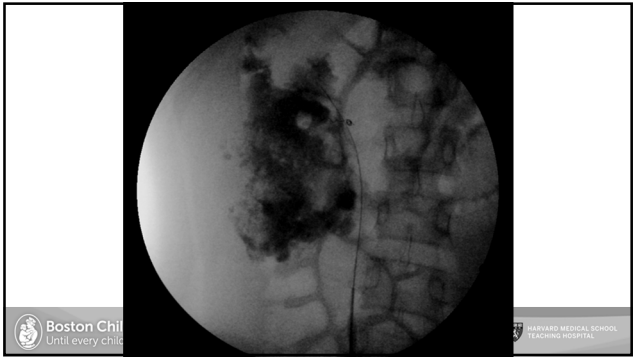
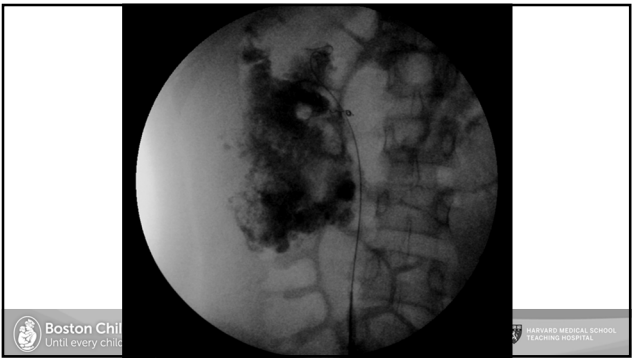
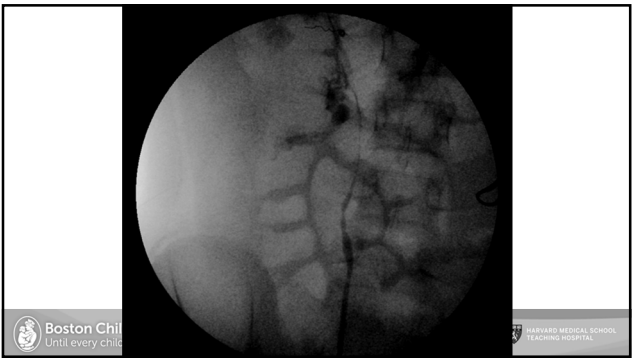
PTD 4

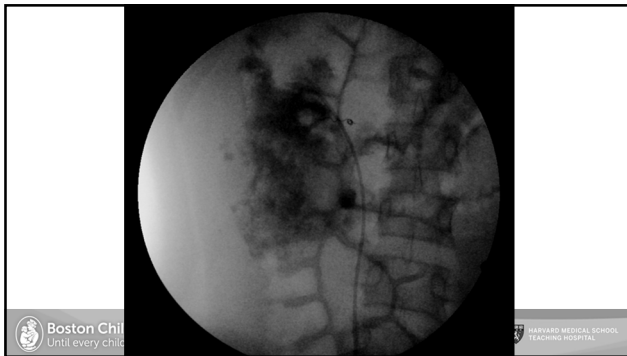
- Intermittently febrile



Next step

- Fevers (initial blood and urine cultures negative)
- Gross hematuria
- Urinary extravasation





Post-procedure

- Stent and bladder drainage for several days
- Fevers abated
- Was empirically on antibiotics and urine culture eventually grew mixed gram negatives
- Experts suggest continued antibiotic prophylaxis to avoid seeding the hematoma or devitalized fragments

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6 weeks

- No hydronephrosis
- Some loss of volume

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Stent removed – 6 week postop CT

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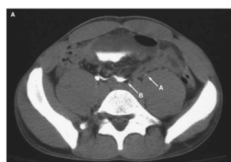
Lower Tract Trauma

Ruptured augment

- A *form* of trauma – typically a traumatic catheterization not permitting bladder drainage
- Always an intraperitoneal rupture
- There are case reports of conservative management
 - I have heard of only one personally, which failed after 8 weeks of drain output!
- Mortality traditionally is around 3%
- If they have a peritoneal shunt, we externalize before exploration

Ruptured augment, continued

- No evidence that CT is superior
- If plain fluoroscopic study is done, must obtain post-drainage films
- If using CT, must dilute contrast
- In either case, fill to known capacity, or edge of discomfort



Management of delayed bladder augmentation perforation
Woodward Adams and Linda M. Finkelstein

Distal Urethra/Bladder Neck

- A very difficult problem (more common in children)
- Repair them immediately!
- Prepare the family for a difficult recovery
 - Neither boys nor girls achieved complete continence
 - Artificial urinary sphincters often eroded
 - Bladder neck slings often caused retention

Long-term continence outcomes after immediate repair of pediatric bladder neck lacerations extending into the urethra. J Urol. 2007 Oct;178(4 Pt 2):1816-8; discussion 1818.

Reminders regarding extraperitoneal rupture ...

- Observation with catheter drainage is acceptable
- Bony spicules in/toward bladder or need for orthopedic hardware requires repair
- You *must* repair injuries in the setting of vaginal or rectal lacerations
 - Standard with suspected vaginal or female urethral injuries is urethroscopy/vaginoscopy and primary repair if possible

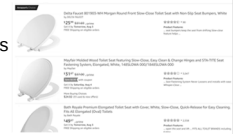
Bicycle Injury

- 12 yM
- Unhelmeted Cyclist
- Riding downhill without brakes, handlebar struck pubis.
- Outside report of blood at meatus, patient denies
 - Neg RUG, Cystogram, CT with delays



The "Penile Slam Syndrome"

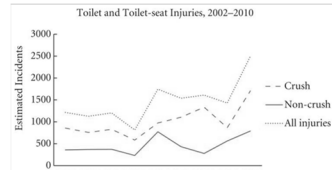
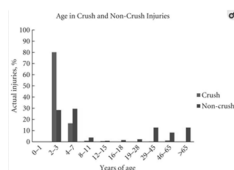
- Toilet seat injuries in children
- "Of crush injuries, 81.7% occurred in children aged 2-3 years and 99.3% occurred in the home"
- Ways to mitigate it:
 - U-shaped (commercial style) toilet seats
 - Slow-close devices



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Frequency of Toilet Seat Injuries



No small slam: increasing incidents of genitourinary injury from toilets and toilet seats. BJUI 2013

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How to Manage Them?

- As with all wounds, ensure Td status (all vaccinated children should be up to date)
- Most children will require sedation
 - Ketamine, benzodiazepines, inhaled agents
- Locally numb wound
- Irrigate
- Close – may only require dermabond (I prefer absorbable)

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An important aside on EW sedation

- It appears to be safe
- Pediatrics, 2006
- *Voluntary* participation in a consortium showed in over 30,000 encounters in 26 institutions that the adverse event rate was low
 - About 1.5% of children had desaturations
 - Laryngospasm occurred in 0.04% of cases

Incidence and Nature of Adverse Events During Pediatric Sedation/Anesthesia for Procedures Outside the Operating Room: Report From the Pediatric Sedation Research Consortium

Joseph P. Conway, MD, George J. Miller, MD, Michael R. Hays, MD, David M. Goffman, MD, James M. Manning, MD, David H. Hamilton, MD, David L. Cohen, MD, and the Pediatric Sedation Research Consortium

Adverse Event	No. of Cases	% of Cases
Desaturation	45	0.15
Apnea	117	0.39
Stridor	107	0.36
Laryngospasm	1	0.003
Seizure	23	0.08
Aspiration	10	0.03
Unresponsive	20	0.07
Recovery	10	0.03
Regurgitation	10	0.03
Other	10	0.03
Total	300	1.00

Sedation safety, continued

- Most were NPO
- Most procedures were just LPs
- These were motivated institutions in the study – if you sense unease, be conservative

NPO for liquids, h	%	#	95% CI
<2	1.8	426	1.3-2.6
2-4	23.8	5386	22.4-26.4
4-6	18.8	4227	16.8-21.8
6-8	16.8	3732	15.3-18.8
8-10	16.8	3732	15.3-18.8
Missing	3.2	875	2.8-3.8

were no deaths. Cardiopulmonary resuscitation was required once. Less serious events were more common with O₂ desaturation below 90% for >30 seconds, occurring 177 times per 10 000 sedations. Stridor and laryngospasm both occurred in 4.3 per 10 000 sedations. Unexpected apnea, excessive secretions, and vomiting had frequencies of 24, 41.6, and 47.2 per 10 000 encounters, respectively.

Testis Rupture

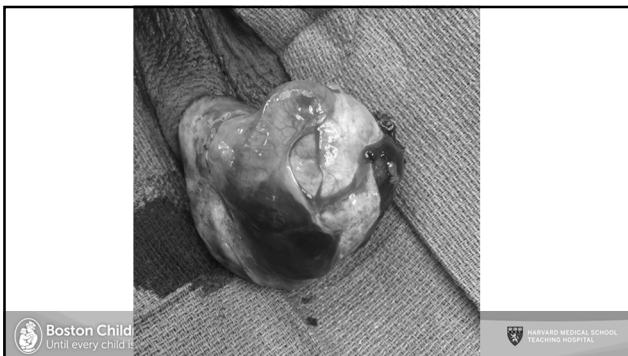
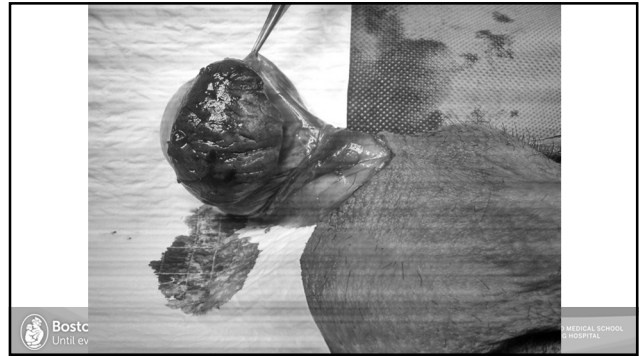
- Rare in prepubertal children, common in adolescents
- Especially common in ball-sports without use of cups (lacrosse)
- Requires a tremendous amount of force, estimated at 50N
 - Origins of this are murky (Wesson, Urol Cutaneous Rev, 1946)

TRAUMATISM OF THE TESTICLE; REPORT OF A CASE OF TRAUMATIC RUPTURE OF A SOLITARY TESTICLE.

MILEY B. WESSON, M.D.
San Francisco, California

them. Injury is not expected in these organs except in the rare situations when it is not possible for them to slip aside due to the rapidity of movement or the large size of the traumatic violence. Since it requires 50 kilos to rupture a testicle, lacerations of the tunica albuginea have been found to be a very rare complication. When there is a history of gonorrhea or renal tuberculosis one must always look askance upon the possibility of trauma playing a part in causing a swollen testicle.





A Conservative Approach to Testicular Rupture in Adolescent Boys

Jimena Cubillos, Edward F. Reda, Jordan Gittlin, Paul Zelkovic and Lane S. Palmer*

From the Division of Pediatric Urology, Cohen Children's Medical Center of New York-Long Island Jewish Health System, New Hyde Park and Westchester Medical Center (EPH, P.D., Valhalla, New York)

- 7 adolescents with testis rupture at 1-5 days post-injury
- All had testicular blood flow at time of injury
- None underwent operation
- All healed, and only one required operation for persistent hemocele
- None had atrophy

but ...

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- Questions remain about timing of recovery
- In this series no boys were hospitalized or given anything stronger than codeine, but two boys were "out of sports for 2-3 months"
- I have a single case of a 12yM persistent unwellness with a large hemocele 6 days out from injury

Chemoprophylaxis for DVT

- Use of low-molecular-weight heparin chemoprophylaxis in adults is common
- It is quite rare in children, and we generally don't use it in our renal trauma population, preferring early ambulation and sequential compression devices on the lower extremities

Venous Thromboembolic Events in Pediatric Trauma Patients: Is Prophylaxis Necessary?
Michelle C. Asz, MD, Jane E. McCormack, RN, Richard J. Scriven, MD, John S. Brebbia, MD, Marc J. Shapiro, MD, and Thomas K. Lee, MD

Table 1 Group characteristics

	Group I (Age <13 years)	Group II (Age 13-17 years)	Group III (Age >17 years)	p value
Total patients	2,320	1,025	10,549	
Total with DVT/PE	2 (0.09)	2 (0.20)	47 (0.54)	0.0007*
Overall mortality	1 (0.04)	25 (2.43)	511 (4.84)	<0.0001*
Mortality of those with DVT	NA	0 (0.00)	9 (19.78)	0.542

Table 2 Description of groups

Group	Age (years)	Admission Services	Chemical Prophylaxis	Mechanical Prophylaxis/SCD
I	0-12	Pediatric services, pediatric surgery	None	Used only on adult-sized 12- and 13-year-olds
II	13-17	Trauma surgery, pediatric surgery	Mixed	Used by most services
III	>17	Trauma surgery	Yes, unless contraindicated	Routine use of SCD, unless contraindicated
		Other adult surgical service		

Table 3 Severity of injury by group and by thromboembolic event

ISS	Group I (Age <13 years)		Group II (Age 13-17 years)		Group III (Age >17 years)		p Value
	Total	VTE (%)	Total	VTE (%)	Total	VTE (%)	
0-9	1627	0	655	0	7,091	28 (0.39)	0.011*
10-15	158	0	105	0	1,025	3 (0.29)	0.721
16-24	181	0	122	0	1,158	12 (1.04)	0.227
25	77	0	115	0 (1.74)	1,075	14 (1.30)	0.546
Unknown	547	0	27	0	197	0	
Total	2,320	0	1,025	2	10,549	57	

*Significant difference.

DVT prophylaxis

- Note that an isolated renal injury of grade 4 or less will render an ISS of 16 at maximum
- No patients under 17 years of age experienced a DVT with this score
- Moreover, even those over 17 years old had a probability of DVT of approximately 1%

Prophylaxis against venous thromboembolism in pediatric trauma: A practice management guideline from the Eastern Association for the Surgery of Trauma and the Pediatric Trauma Society
Arash Mahajerin, MD, MSC, John K. Petty, MD, Sheila J. Hanson, MD, MS, A. Jill Thompson, PharmD, Sarah H. O'Brien, MD, Christian J. Strick, MD, Toni M. Petrillo, MD, and E. Vincent S. Fannin, MD, MHS, Chicago, California

• “Conditionally recommend PPx for older, severely injured children at low risk of bleeding

• Mechanical ppx for older children

PKCO Question 1
In children hospitalized after trauma who are at low risk of bleeding, we conditionally recommend pharmacologic prophylaxis be considered for those >15 y old and in younger prepubertal children with ISS >25. We conditionally recommend against the use of routine pharmacologic prophylaxis in prepubertal children, even with ISS >25.

PKCO Question 2
In children hospitalized after trauma, we conditionally recommend mechanical prophylaxis be considered for those >15 y old and in younger prepubertal children with ISS >25 versus no prophylaxis or in addition to pharmacologic prophylaxis.

PKCO Question 3
In children hospitalized after trauma, we conditionally recommend against active surveillance for VTE with ultrasound compared with daily physical examination alone for earlier detection of VTE.

Takehomes #1

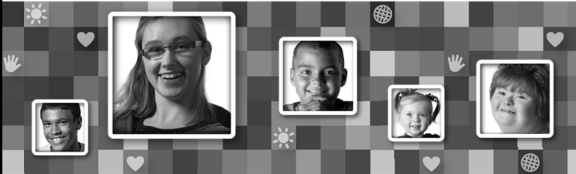
- Renal trauma – most grade 4 injuries will not require intervention
- Staging with 1,2,3 ... 5, and everything else is grade 4
– Recall that “shattered kidneys” and “devitalized fragments” are not in the staging algorithm
- The solitary kidney – be reasonable! Overall risk is low, and use as opportunity to maximize overall health
– Seatbelts, ATV avoidance, nephrology follow-up

Takehomes #2

- Bladder neck injuries in children more commonly involve the urethra than in adults
– Stage bladder and urethra, repair combined injuries immediately
- Testis – observing rupture is possible, but use your judgment. Time to return to wellness remains in question
- Emergency ward sedation allows for repair of nearly cutaneous genital injuries



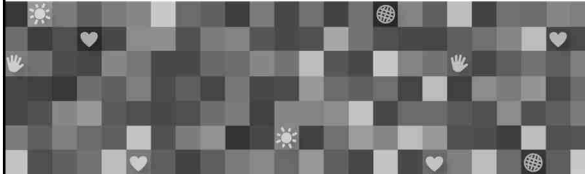
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Disclosure Statement



Nothing to disclose

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Pediatric Oncology

- Overall childhood cancer survival rate >70%
 - Price of survival= more “intensive” protocols= long term adverse sequelae
- 1:450 young adults in USA is childhood cancer survivor
 - CCSS: > 73.4% will have a chronic health problem prior to age 40 & 1/3 of them are life threatening
 - 18.1% cumulative mortality rate @ 30 yrs from dx

- Oeffinger KC et al. NEJM 355:2006.

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COG

- Developed long term f/u guidelines to determine late effects in survivors
- Issues:
 - Patients often aren't aware or don't comply with f/u
 - Lack detailed knowledge of prior treatment
 - Result is that many patients do not receive appropriate screening & treatment based on prior exposure & cumulative risks

- Taylor A et al. Int J Cancer, 22:2008.

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Risks

- Childhood GU malignancy survivors:
 - Prone to organ specific malfunction due to surgery, chemo, +/- XRT
- Non- GU malignancy survivors:
 - Secondary problems of CKD, SMN, reproductive & bladder dysfunction
 - Risk factors: age, sex, genetics, XRT, alkylating agents (CPM)

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Gonadal Function

- Prepubertal testis is less vulnerable to injury than postpubertal testis
 - Prepubertal germ cell damage can occur oligo-azospermia
 - Leydig cells, most resilient → rare androgen deficiency
- Prepubertal ovaries (greater follicle complement)- rarely radio-resistant compared to adults
 - >20 Gy XRT → permanent ovarian failure & premature menopause
 - Uterine XRT → increased adverse pregnancies

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Risk of Secondary Malignancy

- 3-6% @ 20 yrs from dx (6-10 x gen pop' n) & increases with time
 - WT – cumulative risk 12.2% @ 50 yrs
- 2nd most common cause of death in survivors
- Secondary leukemias- alkylating agents & topoisomerase II inhibitors (etoposide, doxorubicin)
 - Short latency: 2-3 yrs after topo & 5-10 yrs after alkylators
- Secondary solid tumors- increased with XRT (10 yr latency)- bones, breast, thyroid, CNS, skin

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Risk of Secondary Malignancy

- GU, H&N, lung & GI tumors occur with more prolonged f/u
- Independent risk factors (adjusted for XRT): female, younger pt, alkylators
- RCC- most common SMN in neuroblastoma survivors (CCSS)
- Bladder tumors- after CPM

- Frobisher C et al. BJU Int. 106:2010.

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CKD

- Cisplatin & Ifosfamide → tubular damage
- WT- ESRD risk @ 20 yrs: 15% in bilateral & 1.3% in unilateral
 - >70% Denys- Drash Sx (early)
 - >40%- WT/aniridia

- Lange J et al. JUrol 2011

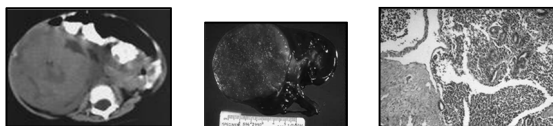
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Bladder Dysfunction

- CNS tumors & pelvic tumors- secondary to primary disease +/- effects of surgery, XRT, chemotherapy
- RMS
 - Bladder preservation protocols require XRT → Many survivors with poorly functioning bladders → abnormal voiding, incontinence
 - UDS- ↓FBC & ↓compliance

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Wilms' Tumor

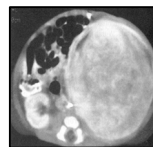
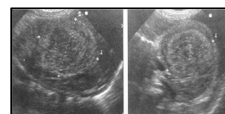


A success story of multimodal therapy & multicenter, cooperative studies!

- Universally fatal at turn of 20th C.
- >90% survival in the 21st C.

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Wilms' Tumor



- Most common GU tumor in children
 - 6% of childhood neoplasms
 - 6-7:1,000,000 children
 - M=F
- 75% - age < 5 y/o
 - Peak age 3-4 in sporadic, unilateral WT- younger in syndromic & bilateral disease (75% < 5 y/o)
- Blacks > Whites > Asians
- Rhabdoid and clear cell sarcoma are no longer categorized as WT variants

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Wilms' Tumor

- 5% bilateral
- 12% multi-focal
- MCDK: only 3 WT in > 7,000 cases
(NWTs IV--- ie: risk is at most 1:2,000 cases)

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Clinical Presentation

- Painless abdominal mass in healthy appearing child
- <15% hematuria
- Hypertension less common than congenital mesoblastic nephroma

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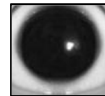
Imaging

- Can alter therapeutic approach
 - Bilateral
 - Solitary or abnormal contralateral kidney
 - IVC extension
- In general initial RUS (with assessment of IVC) with confirmatory CT of chest & abdomen

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Genetic Issues

- Predisposing Syndromes (10% of WT vs Sporadic- 90%):
 - WAGR
 - Beckwith- Weidemann
 - Denys-Drash
 - Hemihypertrophy, hypospadias & UDT, & aniridia
- 11p13, 11p15 & 16q & 1p chromosome loci identified to be important in syndromic WT; gene mutations found in < 10% sporadic WT



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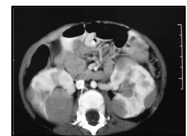
Syndromes & Risk of Wilms' Tumor

- | | |
|---|---|
| •High risk (>20%) <ul style="list-style-type: none"> • WT1 deletions (including WAGR syndrome) • Truncating and pathogenic missense WT1 mutations (including Denys-Drash syndrome) • Familial Wilms tumour • Perlman syndrome • Mosaic variegated aneuploidy • Fanconi anaemia D1/Biallelic BRCA2 mutations | •Moderate risk (5-20%) <ul style="list-style-type: none"> • WT1 intron 9 splice mutations (Fraser syndrome) • Beckwith-Wiedemann syndrome • Simpson-Golabi-Beckwith syndrome caused by GPC3 mutations/deletions |
| | •Low risk (<5%) <ul style="list-style-type: none"> • Isolated hemihypertrophy • Bloom syndrome • Li-Fraumeni syndrome |

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Pathology

- 2 variants:
 - Favorable (FH)- classic triphasic pattern of blastema, stroma, epithelial (tubular) components
 - Unfavorable (UH)- Anaplastic
 - Focal and diffuse patterns
 - 10% of WT but 60% of deaths
- Nephroblastomatosis- presumed "blastemal" precursor lesion
 - <1% non WT autopsy kidneys
 - 45% in unilateral WT
 - 100% in bilateral WT



Nephroblastomatosis variations



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Nephrogenic Rests

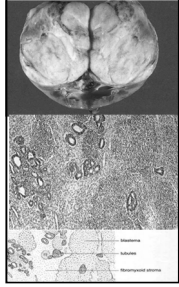
- ILNR (intralobar):**
 - Earlier in development, less common
 - Associated with early dx WT & syndromes- WAGR, Denys-Drash
- PLNR (perilobar):**
 - Present later
 - BWS, hemihypertrophy




WT : Pathology

FH: Classic triphasic pattern

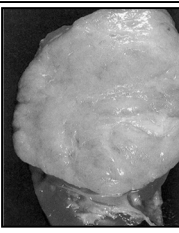
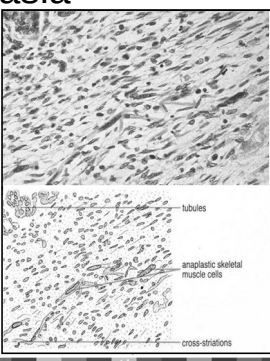
- Epithelial (tubules)
- Blastemal (small blue cell clusters)
- Stromal (mature mesoderm-ganglion, muscle, cartilage)



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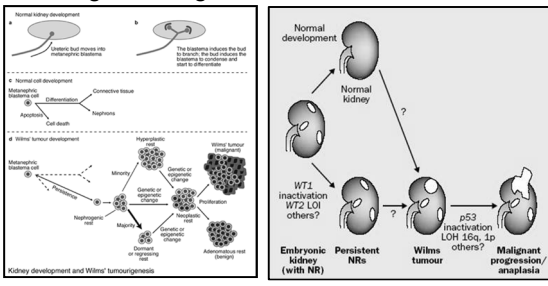
Anaplasia

UH: Anaplasia (focal/diffuse)

tubules
anaplastic skeletal muscle cells
cross striations

Putting It All Together

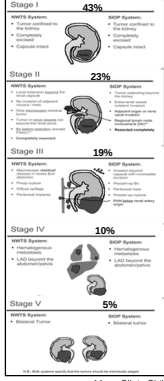


Normal development
Normal kidney
WT1 inactivation
WT2 LOI
others?
Embryonic kidney (with NR)
Persistent NRs
Wilms tumour
p53 inactivation
LOI 10q, 1p
others?
Malignant progression/anaplasia

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WT Staging

- In America (NWTs)- surgical (whereas SIOP -imaging)
- I - Confined tumor, total resection
- II - Outside capsule (bx, spill), total resection
- III - Incomplete resection, massive spill, + LN
- IV - Distant mets (hematogenous)
- V - Bilateral tumors**



Stage I 43%
Stage II 23%
Stage III 19%
Stage IV 10%
Stage V 5%

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WT Surgery-Unilateral Tumor

- Transperitoneal
- Contralateral exploration 1st
 - Not Mandatory if fine CT negative
- Ipsilateral nephrectomy with LN sampling
- Bx only if potential for damage

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Bilateral WT Surgery

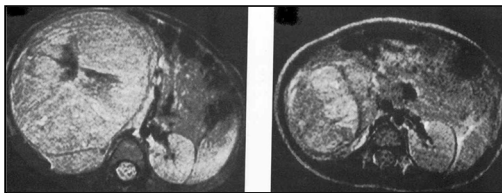
- Up Front Chemo
- Bx for inconclusive tumors, unless small lesion amenable to "easy" PNx
- @ 2nd look excise if >2/3 kidney can be preserved
- Nx only if known UH or chemo failure
- Prognosis=higher staged unilat WT

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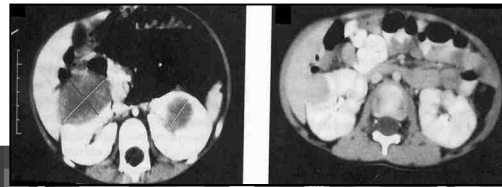
WT : Downstaging With Chemotherapy

- Not yet routine in USA- NWTSG/COG
- Current indications:
 - Bilateral
 - Major vascular invasion
 - Unresectable/ risk to contiguous organs
- Up front chemotherapy-SIOP

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Pre & Post chemotherapy allows renal preservation



Partial Nephrectomy

- SIOP: no recommendations
- NWTSG: bilateral WT, nephroblastomatosis, solitary kidney, renal insufficiency
 - risk of renal insufficiency/failure & metachronous tumors along with excellent survival & low recurrence rates in patients with bilateral WT (& RCC in adults)---Why not partial nephrectomy?



Horwitz,1996
McLorie,1991
Moorman Voestermans,1991

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Surgery For WT

- 11% surgical complication rate (Ritchey, J Urol, 1997)
 - Hemorrhage & bowel obstruction most common
- Spillage & rupture increases local recurrence rate by factor of 6 (Shamberger, Ann Surg, 1998)

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Long Term Concerns

- Adult survivors:
 - 20% CHF rate in those >20 yrs out who have received doxorubicin (Green, J Clin Oncol, 2001)
 - Increased 2nd tumor risk including non WT- renal tumors in remaining kidney (Breslow, J Clin Oncol, 1995; Cherullo, J Urol, 2001)

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NWTS III

Stage	Histology	Survival(%)
I	FH	97
II	FH	92
III	FH	84
IV	FH	83
I-III	UH	68
IV	UH	55
All	FH	89
CCSK	-	75
Rhabdoid	-	26

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Survival

NWTSG	4yr DFS	4yr OS
Stage I	89%	95.6%
Stage II	88%	91%
Stage III	-	91%
Stage IV	-	80%
SIOP	2yr DFS	5yr OS
Stage I	88%	93%
Stage II	84%	88%
Stage III+	71%	85%

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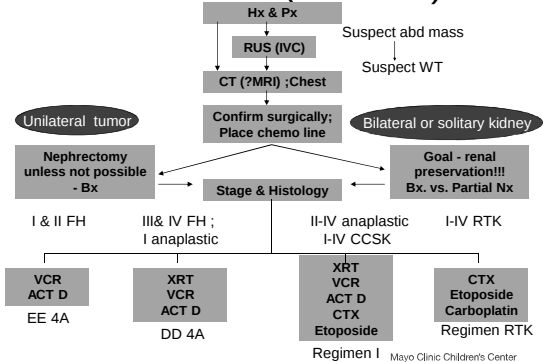
NWTS V Protocol

Stage	XRT	Chemo
I/II FH/UH	-	EE-4A
III/IV FH	+	DD-4A
II-IV, focal anaplasia	+	DD-4A
II-IV, diffuse anap.	+	Regimen 1
I-IV CCSK/rhabdoid	+	Reg. RTK

- EE-4A= dactinomycin, vincristine
- DD-4A= dactinomycin, vincristine, doxorubicin
- Reg. 1= dactinomycin, vincristine, doxorubicin, cyclophosphamide, etoposide
- Reg. RTK= carboplatin, etoposide, cyclophosphamide

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WILMS' TUMOR (NWTS-5)



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Other Renal Tumors

- Renal cell carcinoma
- Multilocular cystic renal tumor
- Clear cell sarcoma
- Rhabdoid tumor
- Renal medullary carcinoma
- Ossifying renal tumor of infancy
- Lymphoma.
- Nephroblastomatosis
- Mesoblastic nephroma
- Angiomyolipoma,
- Metanephric adenoma,

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Other Malignant Renal Neoplasms

- Clear Cell Sarcoma of Kidney:
 - “Bone metastasizing renal tumor of childhood” - 50% with mets @ dx
 - Prone to brain mets as well
 - Marked improvement in survival (90%) with doxorubicin Rx
- Rhabdoid
 - Infants
 - Brain mets - common
 - Dismal prognosis

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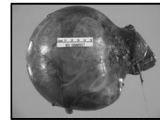
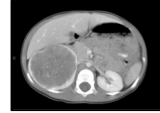
Congenital Mesoblastic Nephroma

- Most common solid renal tumor in infants < 3 mos.
- Like WT, can be dx antenatally but no distinguishing features
- Nephrectomy usually curative
- Cellular variants & incomplete resection can behave aggressively- ?? Chemo??

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Renal Cell Ca

- Mean age- 5 yr
- < 5% of all RCC
- Better survival than adults- 75% 5 yr survival
- Increased frequency in survivors of WT & neuroblastoma ----?? possible genetic predisposition rather than a SMN (more like MEN)??



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Neuroblastoma- Epidemiology

- Most common extracranial solid tumor of childhood
- 1 per 10,000 children
- 750 new cases/yr (US + Canada)
- Male: female ratio of 1.3:1
- Most sporadic, 1-2% familial

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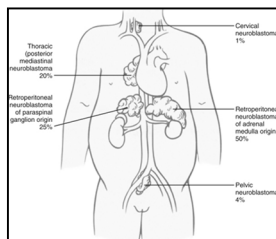
Neuroblastoma

- 8-10% of childhood neoplasms
- Neural crest cells: form SNS & adrenal medulla
- SNS tumors develop along 2 lines: pheochromocytoma & sympathoblastoma
(neuroblastoma --- ganglioneuroblastoma --- ganglioneuroma)
- VMA screening in Japan & Canada has led to increase in dx but no change in survival (neuroblastoma in situ-spontaneous regression)
 - Mass screening will not affect outcome (Woods: Lancet. 348:1682, 1996)

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Presentation

- 65% retroperitoneal; 40% adrenal
- 4% presacral (pelvic) location & can compress bladder--voiding symptoms (so can WT, sarcomas, teratomas)



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Neuroblastoma : Presentation

- Unlike WT, often cross midline
- Unlike WT, often sickly appearance
- 70% present with mets:
 - infants-25% with mets-liver, soft tissue
 - < 1 y/o- 68% mets- bone & BM
 - 50% have anemia from BM involvement
 - <55 paraneoplastic symptoms
- 20% inherited?

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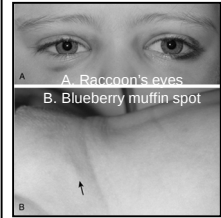
Neuroblastoma & Biochemistry

- Unlike pheochromocytoma - norepinephrine cannot be converted to epinephrine (VMA is metabolite of both)
- Catecholamines related symptoms:
 - paroxysmal HTN, flushing, palpitations, headaches (reported to occur in pregnant mothers of affected fetuses)

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Clinical Presentation

- Abdominal Mass
- Bone pain (difficulty with ambulation)
- Anemia
- Raccoon's eyes (hemorrhage in periorbital mets)
- Weight loss, fever, hypertension
- Opsoclonus-myoclonus



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Opsoclonus-Myoclonus

- Opsoclonus – rapid eye movements (dancing eyes)
- Myoclonus – uncontrolled jerky movements in the extremities (dancing feet and hands)
- Cerebellar ataxia, dysphasia, intellectual deficit, vomiting
- Immunological basis
- No improvement once it occurs, even in survivors

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Initial Workup

- Labs:
 - CBC, Chem, Ferritin, LDH
 - Urinary catecholamines (VMA, HVA)- spot pos in >75% (24 hr urine- >95% pos)
 - Bone marrow- 70% pos
- Imaging
 - Ultrasound
 - CT
 - Bone scan
 - MIBG
 - MRI – spine involvement

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CT: Wilms vs Neuroblastoma

Wilms

- Emanating from within kidney ("clawing")
- Solid/cystic
- Pushes away vessels
- Lymph nodes +/-
- Pulmonary mets
- Vascular thrombus

Adrenal Neuroblastoma

- Compresses kidney
- Calcifications
- Encases vessels
- Lymph nodes +>-
- Bony mets
- Vascular invasion/compression

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Surgical Staging

- Diagnosis may be made with imaging, catecholamines and bone marrow aspiration
- Usually open vs laparoscopic biopsy is required
- Upfront resection only if very small localized lesion
- Biopsy, BMA/Bx, Central line

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Surgical Approach (Initial)

- Laparoscopic or open biopsy
 - At least 1 cubic cm of tissue (fresh)
 - Primary resection acceptable only if very small (limited primary adrenal, mediastinal)
- Thoracoscopic resection for mediastinal masses
- Extended subcostal vs thoracoabdominal incision

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INSS – International Neuroblastoma Staging System

- Stage I – Localized tumor
- Stage 2a – unilateral tumor with gross total resection (GTR), lymph nodes (-)
- Stage 2b – unilateral tumor with GTR, ipsilateral LN (+), contralateral LN (-)
- Stage 3 – Crosses midline or with contralateral LN (+)
- Stage 4 – distant LN, bone marrow, bone, liver (except 4S)

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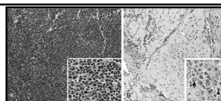
Stage 4s

- Baby < 1 yo (maybe up to 18 mos)
- Stage 1 or 2 local disease
- Widespread dissemination limited to liver, skin, or bone marrow (less than 10% tumor cells in marrow)
- Excellent prognosis with spontaneous resolution
- Early morbidity from respiratory embarrassment

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Histopathology

- Neuroblastoma vs ganglioneuroma vs ganglioneuroblastoma
- Small round blue cells (frozen unhelpful)
- Homer-wright pseudo-rosettes
- Mitosis-Karyorrhexis index (MKI)
 - Modified Shimada criteria
 - Favorable vs unfavorable



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Neuroblastoma Risk Profiles (Brodeur)

Feature	Type 1	Type 2	Type 3
MYCN amp	No	No	Yes
DNA ploidy	Hyperdiploid	Near diploid	Near tetraploid
LOH	Rare	25-50%	Yes
Neurotrophin	High	Low/absent	-----
Gene Expression	(except TRK-B, high)		
Age	< 1 y/o	>1 y/o	-----
Stage	1,2, 4S	3,4	-----
3 yr survival	95%	25-50%	<5%

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Risk Status

- Age
- Stage (INSS)
- Histopathology
- Biologic Variable
- Risk factors (INRG/ International Neuroblastoma Risk Group)

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Low Risk

- Stage 1 or 2
- Asymptomatic stage 4s
- GTR
- N-myc negative, no diploidy, favorable histology
- Surgical resection is curative, no adjuvant therapy necessary
- Survival 97%

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Intermediate Risk

- N-myc negative
- Stage 2A/2B, <50% GTR
- Stage 3, <18 mos with unfavorable, >18 months with favorable histology
- Stage 4, <12 mos unfavorable or 12-18 mos with diploidy and favorable
- Stage 4s symptomatic or diploidy or unfavorable

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Intermediate risk treatment

- Chemo – Cisplatin, Etoposide, Doxorubicin, Cyclophosphamide
- 2 cycles chemo, then re-assessment for resection
- Goal of surgery is > 50% resection
- Avoid resection of vital structures
- Overall survival around 70-90%

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High Risk

- Stage 2a/2b; N-myc amplified
- Stage 3; N-myc amplified or N-myc (-) but unfavorable histology
- Stage 4; N-myc amplified or >18 mos or diploidy or unfavorable
- Stage 4s with N-myc amplified

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High risk treatment

- Chemo at higher doses
- Restage at 2, then 4 cycles
- Surgical goal of at least 50% GTR (preferably >90%, but avoid injury to vital structures)
- Radiation
- Peripheral stem cell transplant
- Retinoid acid
- Monoclonal antibody therapy against GD2
- Survival 20-40%

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Surgical approach in intermediate & high risk patients

- Extended subcostal vs thoracoabdominal incision
 - Identify great vessels
 - Vessels can be extremely distorted
 - Gross resection >50% (preferred >90%)
 - Bivalve tumor over vessels
 - Better to leave tumor than compromise vital organs (including kidney, spinal nerve roots)

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Rhabdomyosarcoma

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Rhabdomyosarcoma

- Most common soft tissue sarcoma- 20% GU
- Tumor of mesenchymal origin with evidence of skeletal muscle differentiation
- Bimodal: 2-6 years and 15-19 years (70% occur <10 years, 50% < 5 years)

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Rhabdomyosarcoma- Epidemiology

- 10-15% solid pediatric malignancies
- 1:2,000,000 annually
- M > F
- Black > Caucasian
- 2q37 gene abnormality?
- Spread: local>lymphatic (18%) > hematogenous (10%)

Table 21.1 Risk Factors for Rhabdomyosarcoma

Congenital
Li-Fraumeni syndrome
Neurofibromatosis
Basal cell nevus syndrome
Fetal alcohol syndrome
p53 mutations
Nieman syndrome
Beckwith-Wiedemann syndrome
Cowden syndrome
Acquired
Marijuana
Cocaine
Maternal exposure to radiation
Maternal history of stillbirths

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Rhabdomyosarcoma: Pathology

- Embryonal (ERMS): 90% of RMS & predominates in younger age groups; GU & ENT sites
 - "Sarcoma botryoides" - polypoid variant found in hollow organs
 - 74% 5 yr. survival

Table 51.2 Histologic Classification of Rhabdomyosarcoma

Diagnosis	Histology	Incidence (%) ^a	5-Year Survival (%)	Prognosis
Embryonal, botryoid	Favorable	6	95	Good
Embryonal, spindle cell	Favorable	2	88	Good
Embryonal, NOS	Favorable	49	66	Intermediate
Alveolar, NOS or solid variant	Unfavorable	31	53	Poor
Anaplastic, diffuse	Unfavorable	2	45	Poor
Undifferentiated sarcoma	Unfavorable	3	44	Poor

^aThese incidences in only 94% of accepted cases fall into the sarcoma NOS category because of insufficient or inadequate tissue to make a more specific diagnosis.
NOS, not otherwise specified.

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Rhabdomyosarcoma: Presentation-Site Dependent

- Bladder:
 - Mean age- 3.5 years
 - 2M:F
 - Palpable mass more common than hematuria
- Prostate:
 - Mean age- 3.5 years
 - BOO +/- hydronephrosis
- Female:
 - Vagina- < 2, vulva- 1-19, uterus-adolescence

Table 51.3 Presenting Clinical Features of Rhabdomyosarcoma

Cause of Presenting Feature	Symptoms and Signs
Visible tumor	Abdominal mass
	Polypoid tumor (sarcoma botryoides)
Bladder outlet obstruction	Strangury
Muscular damage	Urinary infection
	Urinary incontinence
	Hematuria
	Vaginal discharge
	Passing tumor fragments

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Rhabdomyosarcoma: Evaluation & Therapy

- MRI (T2 image) -best imaging modality for pelvic tumors.
- Surgery- primarily diagnostic with therapeutic intervention aimed at organ preservation
- Chemotherapy has been mainstay of therapy with diminished role for XRT
 - Clearly cures microscopic disease



TMN-RMS (Pre-operative)

Table 51-6 Intergroup Rhabdomyosarcoma Study Modified TNM Pretreatment Staging Classification

Stage	Sites*	T	Size†	N	M
1	Favorable	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	a	N0 or Nx	M0
3	Unfavorable	T1 or T2	a	N1	M0
			b	N0 or N1 or Nx	M0
4	All	T1 or T2	a or b	N0 or N1	M1

*Favorable sites are the genitourinary system excluding bladder/prostate. Unfavorable sites are the bladder/prostate and retroperitoneum.
 †Pretreatment size is determined by external measurement using MRI or CT, depending on the anatomic location. For less accessible primary sites, CT is used as a means of lymph node assessment as well. Metastatic sites require some form of imaging (but not histologic confirmation except for bone marrow examination) confirmation.



Postoperative IRS Grouping for Rhabdomyosarcoma

Group 1: localized disease, completely excised, no microscopic residual

A: confined to site of origin, completely resected

B: infiltrating beyond site of origin, completely resected
 Group 2: total gross resection

A: gross resection with microscopic local residual

B: regional disease with involved lymph nodes, completely resected with no microscopic residual

C: microscopic local or nodal residual

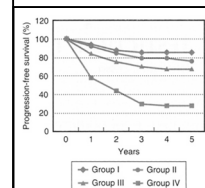
Group 3: incomplete resection or biopsy with gross residual

Group 4: distant metastases



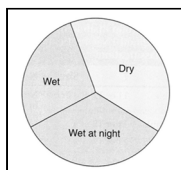
TMN + Postoperative Staging

- Used in IRS IV-V & eliminates prior bias by grouping patients based on completeness of surgical resection
- 80% of bladder/prostate are group III (incomplete resection with gross residual disease)
- > 50% of non bladder-prostate are group I with 20% each in groups II & III



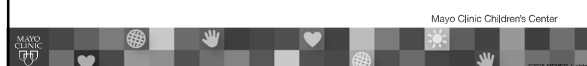
Surgical Therapy

- Initial biopsy & staging with possible multiple looks after adjuvant therapy
- Attempts at organ preserving surgery has made exenteration a rare event!
 - Possible in > 60% v. 25% 30 yrs ago
 - Quality of organs suspect in long run- incontinence, irritative symptoms, site of secondary tumor?



Role of Radiation

- Seemingly more controversial issue for the urologist (due to experience with adult pelvic XRT):
 - Bladder Effects-
 - Irritative voiding
 - Bladder dysfunction
 - Hemorrhagic cystitis & secondary malignancies
 - Proctitis
- Makes interpretation of subsequent pathology more difficult!



Chemotherapy

VAC: cheaper, less toxic & equally effective when compared to VIE (vincristine, ifosfamide, etoposide) & VAE (vincristine, dactinomycin, etoposide)

Crist. J Clin Oncol 19:3091, 2001

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RMS: Risk Stratification

- Low Risk: most vaginal, paratesticular primaries, embryonal primaries with gross total resection, no metastases
- Intermediate Risk: most bladder/prostate primaries, nonmetastatic embryonal, alveolar, or undifferentiated tumors with gross residual disease, metastatic embryonal tumors less than 10 years old
- High Risk: metastatic embryonal tumors more than 10 years old, metastatic alveolar or undifferentiated tumors

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IRS V Chemotherapy

- Low risk disease- randomizes VAC vs VA +/- XRT
- Intermediate risk- compares XRT/VAC vs XRT/VAC alternating with VC + Topotecan
- High risk- XRT/VAC + Irinocetan (CPT-11)

- Raney, 2001

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Treatment Protocols & Outcomes

Clinical group	IRS I	IRS II	IRS III
	Survival (%)		
I-Favorable	81	85	93
II-Favorable	73	88	54 (?)
III-Favorable	70	79	89
I/II Unfavorable	57	71	80
IV	26	27	27
Overall	55	63	71

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RMS : Outcomes & Questions

- Residual masses require bx & close Xray and clinical fu but don't always = residual cancer
- Still controversy regarding findings of mature rhabdomyoblasts- resection (especially if already received maximum adjuvant therapy) vs observation (where a functional organ might be sacrificed)!

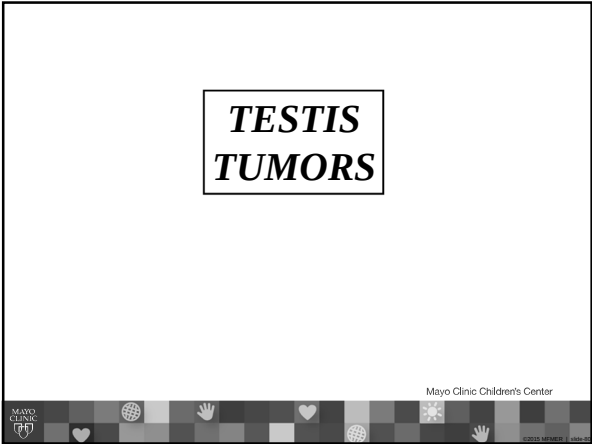
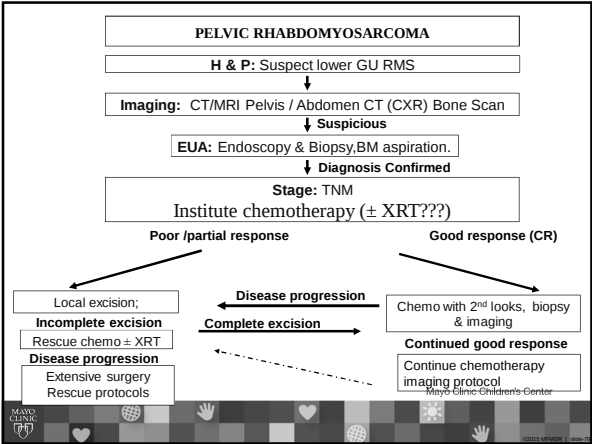
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Relapse

- Survival depends on initial stage and tumor type
 - 5 yr survival 64% for Botryoid ERMS, 26% for non-Botryoid ERMS & <5% non Embryonal RMS

- Pappo: J Clin Oncol 17:3487, 1999

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Testicular Tumors: General

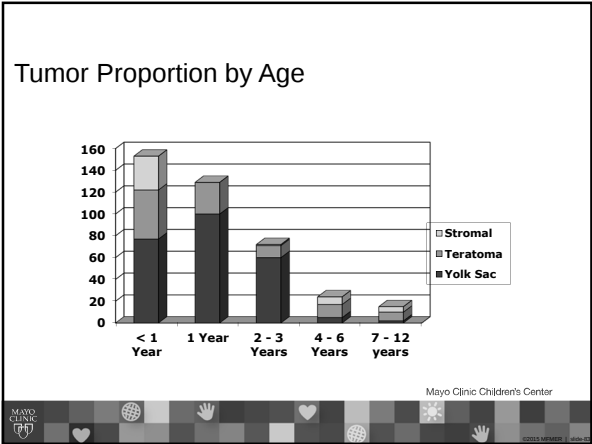
- 2-3: million children
- Only 1-2% of pediatric neoplasms
- Majority < 2 yrs. of age
- Mets (<15%) : LN- 28%, hematogenous- 40%, both- 20%

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Testis and Paratesticular Tumors: Prepubertal

- Kaplan Classification:
 1. Germ cell tumors
 2. Gonadal stromal tumors
 3. Gonadoblastoma
 4. Supporting tissue tumors
 5. Lymphoma/leukemia
 6. Tumor-like lesions
 7. Secondary tumors
 8. Adnexal tumors

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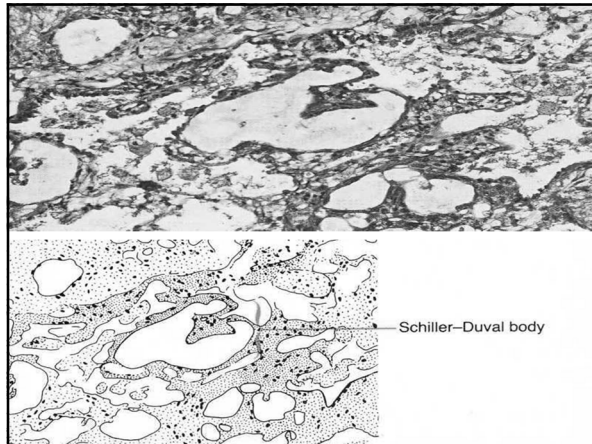


PREPUBERTAL TESTIS TUMORS: ACTUAL PREVALENCE RATE OF HISTOLOGICAL TYPES

HANS G. POHL, ASEM B. SHUKLA, PETER D. METCALF, BARTLEY G. CILENTO, ALAN B. RETIK, DARIUS J. RAGLI, DALE S. HUFF and H. GIL RUSHTON

From the Departments of Urology, Children's National Medical Center, Washington, D. C. (HGP, HGR); Division of Pathology (DSR), Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (ASB); Hospital for Sick Children, Toronto, Ontario, Canada (PSM, DSR), and Children's Hospital, Boston, Massachusetts (HGC, ARB)

	Hospital for Sick Children	Children's Hospital of Philadelphia	Children's National Medical Center	Children's Hospital	Present Series	% Total Cases Testis Tumor Registry ²¹
Yolk sac	4	8	1	2	15	62
Teratomas:						
Mature	19	11	7	6		
Immature	3	1				
Subtotal	22	12	7	6	48	23
Epidermoid Cyst	5	6	2	1	14	3
Gonadal stromal:						
Granulosa		3		2		
Leydig		2	1	1		
Sertoli	2			1		
Mixed		1				
Subtotal	2	6	1	4	13	11
Other:						
Gonadoblastoma	1	1			2	1
Cystic dysplasia		2				
Lymphoma		3	1			
Inflammatory		1	1			
Subtotal	1	6	2		9	
Overall	34	38	13	13	98	298



Yolk Sac Tumors: Diagnosis

- Scrotal mass: usually asymptomatic
 - 10% associated hydrocele
 - 3% + Hx of trauma
- > 85% are localized (Stage I)
- U/S useful if exam difficult or hydrocele present
- Abd & chest (??? vs routine CXR) CT to stage along with AFP

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Yolk Sac Tumors: Markers

- Alpha feto-protein: elevated in 90% with YST
 - T 1/2= 5 days
 - normally elevated (GI tract/liver) from newborn to 8-9 mos. of age
 - especially elevated in premies
- Histologically "pure": Beta-HCG is not useful
 - Produced by syncytiotrophoblast (still usually obtained: T1/2= 24 hrs.)

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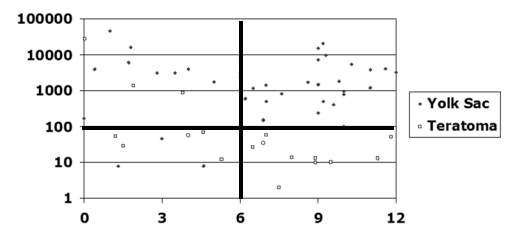
AFP in normal infants



AFP in normal infants



AFP Values in Infants



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Yolk Sac Tumors: Staging

- Stage I:
 - Completely resected localized tumor with normal AFP degradation & negative Xray staging
 - recommended that if markers weren't obtained or initially normal that limited LND vs sampling be done
- Stage II:
 - + microscopic margins (scrotum or cord-includes transscrotal orchiectomy), persistent AFP elevation, +RPLN (<2 cm bulk)
- Stage III:
 - + RPLN (>2 cm) w/o hematogenous/distant mets
- Stage IV:
 - + distant/hematogenous mets

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Yolk Sac Tumors: Role of Surgery

- Radical inguinal orchiectomy: usually curative (>85% Stage I)
- Routine RPLND: not done !!!!! (historically high complication rate & usually negative)
 - Reserved for:
 - Normal or unknown AFP @ dx.
 - Persistent RP mass after chemo
 - Persistent elevation of AFP with negative imaging after chemotherapy

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Yolk Sac Tumors: Chemotherapy

- Platinum based chemotherapy allows similar survival to adults with GST (>90%)
 - Series are small & # with mets extremely small, thus difficult to assess completely
 - Prior to modern chemotherapy- 24 month survival in those with mets: 30-54%

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Teratoma

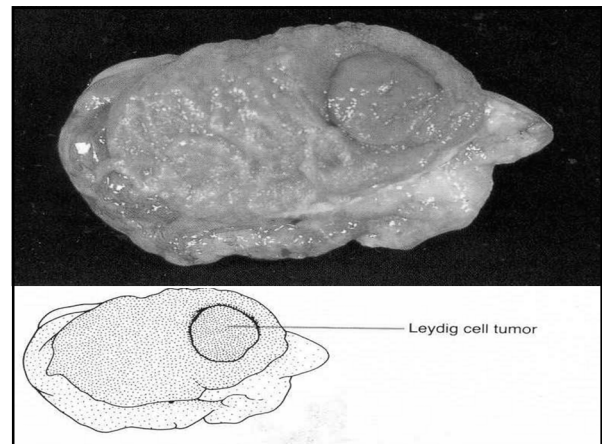
- Usually mature and well differentiated
- Consistently benign in children < 2 years
- U/S appearance of heterogeneous intratesticular mass with internal echoes (calcification) strongly suggestive
- Rx: Enucleation possible

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Leydig Cell Tumor

- Most common gonadal stromal tumor with peak @ 4-5 yrs.
 - 10% of precocious puberty < 9 yrs.
 - Unilateral & benign
- Classic presentation: Triad of precocious puberty, testis mass (sometimes U/S only!!!), & elevated serum T & urine 17 KS
 - Differentiate from pituitary tumors by low LH & FSH
 - Adrenogenital Sx usually bilateral tumors with elevated 17 KS & pregnanetriol & regress with glucocorticoid Rx
- Path : Reinke's crystals rare in children (40% of adults)
- Rx: Enucleation when possible

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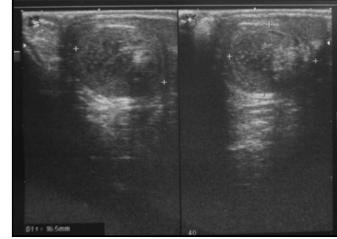


Paratesticular Rhabdomyosarcoma

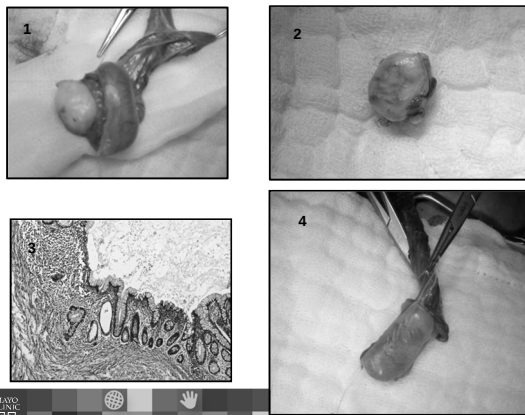
- Histology usually favorable (ERMS) but L.N. + @ dx. in up to 30%
- Routine RPLND no longer recommended when imaging is (-), & primary completely resected
 - controversial benefit in pts. > 10 yrs. because of poorer prognosis in older group
 - sampling done if bulky mass after chemo
- XRT: No longer routine if imaging studies are negative for L.N.
- With chemotherapy alone, survival > 90%

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A Definite Role for Ultrasound in Surgical Planning

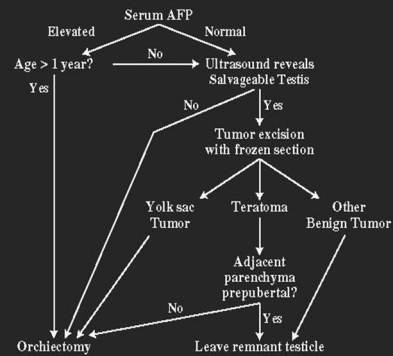


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Surgical Algorithm for Prepubertal Testis Tumors



Gonadoblastoma

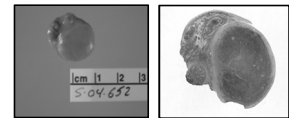
- Develop in patients with an abnormal gonad whose karyotype contains a Y chromosome.(Intersex conditions- gonadal dysgenesis, testicular feminization)
 - 80% phenotypic females with 46 XY
 - 22% streak, 18% dysgenetic, 60% indeterminate
- Bilateral in 10-33%
- Benign tumors - as germ cell elements outgrow stroma, 10-60% will progress to malignant dysgerminoma (seminoma), **after puberty!!!!**

Rx: Gonadectomy(ies) in @ risk patients-early

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Secondary Tumors: Leukemia & Lymphoma

- Testicular involvement:
 - Lymphoma- 4%
 - Leukemia-11-25%

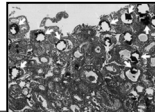
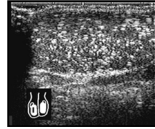


- Up to 60% of ALL pts. with testes involvement have no other evidence of disease (blood-testis barrier, a sanctuary)
- Biopsy only if evidence of testes involvement ; if +, further chemotherapy & gonadal XRT (B.M tpx ?????)

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Testicular Microlithiasis

- “Ball stones” (calcium)
- <.5% of men
- 80% bilateral
- Of an “incidentaloma”
- Relationship with testicular cancer has not been confirmed by in depth studies... but is suggestive
 - Microcalcifications found in 50% of testes tumors, but most men with microlithiasis don't develop cancer
- Recommend- Routine TSE



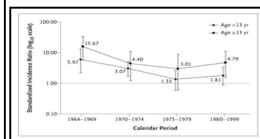
Cryptorchidism & Testis Cancer

Adult risk of Ca. Developing in UDT:

- 35 x that of normally descended testis historically- Likely really only 4-6 x increase!
- inguinal UDT- 1% risk, abdominal- 5% risk
- contralateral descended testis risk:12-20%
- Seminoma- most common tumor
 - Orchidopexy associated with increase in pathological frequency of NSGCT

Cryptorchidism & Testis Cancer

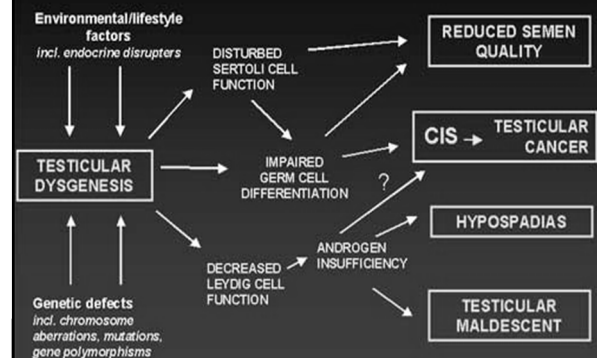
- Swedish cohort
 - 16,983 men after orchidopexy & followed for a total of 209,984 person-yr
- RR of testicular cancer among those who underwent Rx for UDT as compared with the Swedish general population
 - Rx before 13 yrs age: RR 2.23 (95% confidence interval [CI], 1.58 to 3.06)
 - Rx after 13 years of age: RR 5.40 (95% CI, 3.20 to 8.53)
- Conclusion: Rx for UDT before puberty significantly decreases the risk of testicular cancer



Pettersson NEJM, 2007

Testicular Dysgenesis Syndrome

Modified from Skakkebaek et al. Hum Reprod 2001



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Adolescent and Transitional Urology

Carlos R. Estrada, Jr., MD, MBA



Boston Children's Hospital
Until every child is well



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2

Topics

1. Stones
2. Varicocele
3. Testicular torsion
4. Transitional urology



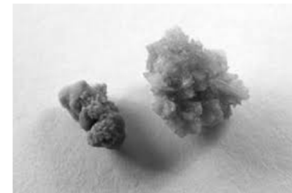
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1. Stones



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Stones - Background

- 1/3000 pediatric admissions in the US (about 2% of all stone disease)
- Boys = girls
- Mean age: 5-7 years
- Higher prevalence in Caucasians
 - ? Increasing incidence
- "Stone Belt"
 - Deep South in North America



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Stones - Composition

- 45-65% calcium oxalate
- 14-30% calcium phosphate
- 13% struvite
- 5% cystine
- 4% uric acid
- 1/3 of pediatric/adolescent stone patients will have an anatomic anomaly of the GU tract



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Stones - Presentation

- Flank pain - 50% (more variable than adults)
- May also have abdominal pain, esp. young children
- Groin or labial pain with ureteral stones
- Gross hematuria - 25-40%
- Microhematuria - up to 90%
- Urinary tract infection - 10-30%
- Incidental imaging findings - 15%
- Nausea and vomiting

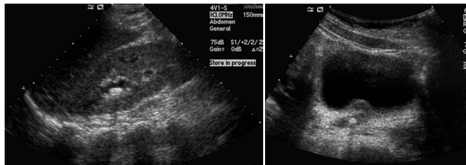
Stones - Evaluation

- Ultrasound Imaging
 - Good for renal and proximal ureter stones
 - 70% sensitivity for stones seen on CT
- But – most missed stones are small (<3mm)
- Highly sensitive for obstruction



Stones - Evaluation

Ultrasound



Stones - Evaluation

CT Imaging

- Radiation exposure
 - Adult abdominal CT: 10 mSv
 - Neonatal abdominal CT: 20 mSv
 - Chest x-ray: 0.01 mSv (DJ Brenner, NEJM, 2007)
- CT should NOT be first imaging modality in pediatric patients with suspected stone disease

Stones - Evaluation

KUB

- Not sensitive in young children
- Abdominal gas obscures view
- No 3D perspective
- X-ray exposure



Stones - Management

- Spontaneous passage is usually preferable
- Small or distal stones more likely to pass
- Large or proximal less likely
 - < 4 mm: 80-90% pass
 - 4-8 mm: 50% pass
 - >8 mm: 10% pass
- Management decisions based on clinical status and stone burden
- The pediatric/adolescent ureter is as compliant as the adult ureter

Stones – Medical Expulsive Therapy (MET)

	Mokhless, 2012 Tamsulosin 0.4 mg/d (>4yrs)	Aydoğdu, 2009 Doxazosin 0.03mg/kg/d	Erurhan, 2013 Doxazosin 0.03mg/kg/d	Tasian, 2014 Tamsulosin [cohort study]
N= drug/control	33/ 28	19/20	24/21	99/99
Age (yrs)	8 ± 7	2-14	7 ± 4	<18 yrs
Stone-free Rate	Drug: 87.8% Control: 64.2% (p<0.01)	Drug: 84% Control: 70% (p>0.05)	Drug: 71% Control: 29% (p=0.001)	Drug: 55% Control: 44% (p=0.03)
Time to passage (days)	Drug: 8.2 Placebo: 14.5 (p<0.001)	Drug: 5.9 Control: 6.1 (p>0.05)	↓ (p=0.001)	N/A

OVERALL + - + +

Stones - Management

When is diversion indicated?

- Evidence of infection
- Fever, chills, wbc, debris in collecting system on imaging, UA, micro
- Severe pain unresponsive to therapy
- Severe nausea unresponsive to therapy
- Solitary kidney
- Drain the obstructed system!



Stones – Medical Management

- Close follow-up is essential
- 1-2 weeks
- Strain all urine when possible
- Immediate re-evaluation if febrile
- If no stone passage within 2 weeks – proceed to surgical treatment
- High-grade obstruction persisting longer than 6 weeks may lead to irreversible renal injury

Stones – Surgical Management

Who needs surgery?

- Ureteral stones that fail medical therapy
- Renal stones:
 - Large stones, staghorn stones
 - Infection-related stones
 - Lifestyle issues (i.e., school, sports)
 - Asymptomatic calculi?
 - >7 mm renal, >4 mm residual fragments after PCNL or ureteroscopy Streeper, 2018

Stones – Surgical Management

- **ESWL** He et al. 2011; Badaway et al, 2012
 - First-line treatment
 - Ultrasound-guided
 - Renal stones – 85 - 95% stone-free rate (SFR)
 - Ureteral stones – 58 - 85% SFR
- **Ureteroscopy**
 - SFR 58 – 100%
 - Higher failure and complication rates in < 6 years old
- **PCNL** Dombrovskiy and Olweny 2018
 - Complication rates 20%

Stones – Long Term Management

- All pediatric/adolescent patients should have metabolic evaluation (24h urine + serum studies: Chem7, PO4, Mg, Ca, UA, 25 Vit D, 1.25 Vit D, PTH)
- Management depends on underlying etiology
- Goals
 - Identify etiology
 - Prevention of further stones

2. Varicocele



Varicocele - Background

"Swollen veins, twisted over the testicle which becomes smaller than its fellow in as much as its nutrition has become defective" - Celsus, 1st Century A.D.

Varicocele – Grading System

- Grade I:** palpable veins with Valsalva; not visible
- Grade II:** palpable veins without Valsalva; not visible
- Grade III:** palpable and visible veins without Valsalva
- Subclinical:** dilated veins on US; non-palpable; Doppler flow reversal

Varicocele - Adults

- Most common reversible cause of male factor infertility
- Noted in 30-40% of men evaluated by an infertility clinic
- Incidence is 15% of all males

80% of men with varicocele are
fertile and asymptomatic

Varicocele - Adolescents

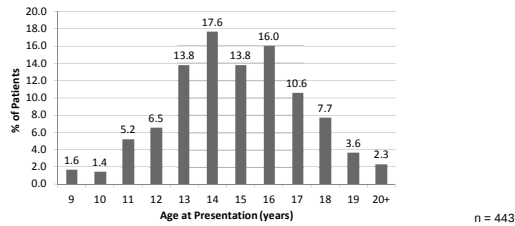
Population: Asymptomatic adolescent males with varicocele and unknown fertility status

Can we select those that would
benefit from surgical correction?

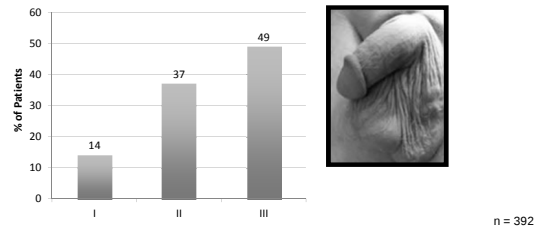
Varicocele - Adolescents

- Prevalence (Akby et al. 2000)
 - 4000 boys
 - <1% in ages 10 years or less;
 - 11% in ages 11-19 years
- Incidence (Steen et al. 1976)
 - >2000 boys
 - 15% (same as adult pop.)

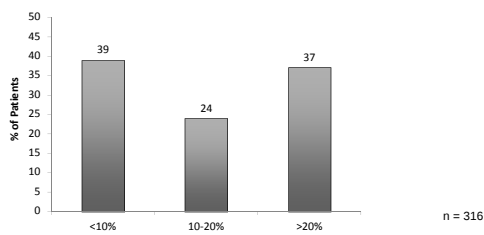
Varicocele – Pediatric Presentation



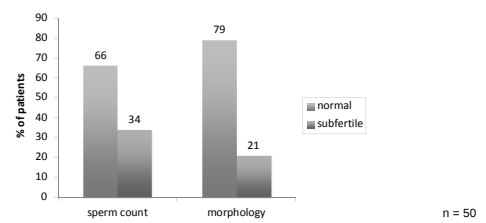
Varicocele – Grade at Presentation



Varicocele – Volume Differential



Varicocele – Semen Analysis in Tanner V



Varicocele – Management in Adolescents



Varicocele – Problem in Adolescents

1. 80% with varicocele - fertile
2. 20% with varicocele - infertile
3. Surgery may benefit 50% of infertile

Therefore, 1 in 10 adolescents benefit from surgery

Varicocele – Indications for Surgery

Common

- Discomfort, pain
- Size (Grade) varicocele
- Hypotrophy, testicular disproportion

Less Common

- Bilaterality
- Solitary testis
- Abnormal semen analysis

Varicocele – Discomfort and Pain

- “Heavy” and “dragging” sensation
- Less common
 - 3% CHB database
- Highest reported incidence
 - 23% surgical series (from NY)

Varicocele – Is Grade Predictive?

- Repair of grade III varicocele results in greater improvement in sperm concentration & motility than Grades I and II... (in infertile men).

No difference in
fertility rates

Steckel et al. 1993

Varicocele – Volume Discrepancy

- May not be varicocele related
- Seen in normal adolescents
- May vary with age & Tanner stage
- Accuracy, consistency in measurement
- Spontaneous improvement
 - $\frac{1}{3}$ to $\frac{2}{3}$ boys with varicocele



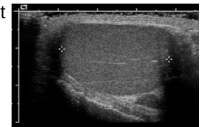
Varicocele – Determining Hypotrophy

- Available tools – variable
 - Calipers, Rulers
 - Orchidometers
 - Rochester, Takihara – (series cut out ellipses)
 - Prader – (12 comparative ovoids)
- Ultrasound calculated volume
 - (Improved Accuracy, Reproducibility)

Diamond et al, 2011

Varicocele – Does Hypotrophy Matter?

- Adult men with varicocele and hypotrophy
 - No correlation between loss of testis volume and fertility Pinto, 1994
 - No difference in mean years trying to conceive Sigman, 1997
- In adolescents, $\geq 20\%$ difference is significant
 - Correlates with poorer total motile sperm count
 - Indication for surgical correction



Varicocele – Semen Analysis

- Important surgical indication for Tanner V
 - Surrogate measure of fertility potential
 - (Ultimate outcome = fertility)
- When considering surgery:
 - Trumps hypotrophy as surgical indicator
 - With normal semen analysis, no need for surgery

Tanner V	Concentration	Motility	Morphology
WHO (subfertile)	< 20 M/mL	< 50%	< 20%

Varicocele – Clinical Dilemma

- Our tools for identifying adolescents at risk for infertility are limited.
- Need to evaluate all apparently meaningful criteria
 1. Relative testicular volumes
 2. Semen analyses
- Need to follow patients prospectively

Varicocele – Surgical Management

- Ligation of spermatic veins
 - Microscopic subinguinal and laparoscopic
 - Lowest risk of recurrence and complications
 - 1 – 3% recurrence/persistence
 - 1 – 10% hydrocele
- Sclerotherapy
 - Tauber's antegrade sclerotherapy
 - Aethoxysklerol 3%
 - 3– 4% recurrence

Choi et al, 2017; Esposito et al, 2018; Paradiso et al, 2016

Varicocele – Putting It All Together

- Adolescent varicocele is a common problem with similar incidence to adult men
- Impact on fertility is unclear
- Ultrasound is superior to PE to quantify testicular volume
- Hypotrophy with >20% size differential, abnormal semen analyses, and pain are indications for surgery
- Surgical approaches same as in adult men

3. Testicular Torsion

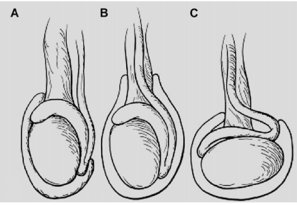


Testicular Torsion - Background

- Most common cause of testicular loss in the US
- Incidence = 1:4,000
- More commonly involves the left testicle



Testicular Torsion - Pathophysiology



From Testis torsion. In: Oldham KT, Colombari PM, Foglia RP, editors. Surgery of infants and children: scientific principles and practice. Philadelphia: Lippincott-Raven; 1997. p. 1552-3.

Testicular Torsion - Presentation

"sudden onset"

"unable to get comfortable"

nausea/vomiting



"gradual onset"

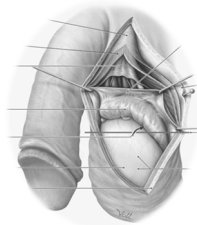
"sore but comfortable"

no problem eating



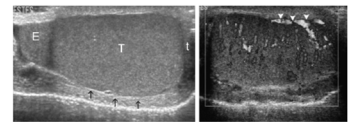
Testicular Torsion - Evaluation

- Abdominal exam
- Inguinal exam
- Scrotal findings
 - Asymmetry
 - Testicular swelling & pain
 - High-riding
 - Absent cremasteric
 - Prehn's sign



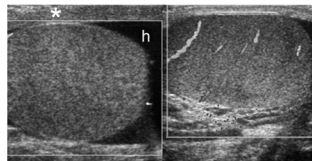
Testicular Torsion - Evaluation

- Laboratory tests
 - Urinalysis and urine culture
- Imaging
 - Ultrasound with Doppler



Testicular Torsion – Sonographic Diagnosis

1. Testicular enlargement
2. Decreased or absent testicular blood flow (Doppler)
3. Parenchymal heterogeneity



Testicular Torsion - Management

- Surgical emergency!
- If your clinical suspicion is high, do NOT delay in order to confirm the diagnosis by imaging.

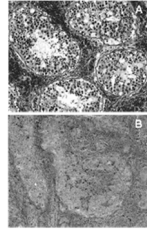
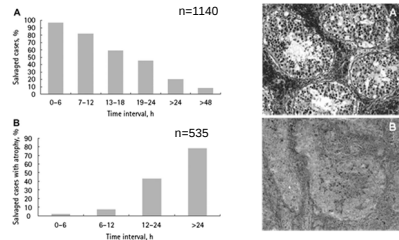


Why? Salvage is TIME sensitive.

Strong clinical suspicion is enough to proceed with scrotal exploration.

6-hour window

Testicular Torsion – Time Sensitivity



Testicular Torsion - Salvage

1. Prompt presentation
2. Prompt diagnosis
3. Immediate surgical exploration



Testicular Torsion - Salvage

- Oxidative stress-induced damage
 - Protective medications?
 - Verapamil, tadalafil, matricaria chamomilla, erdoesteine, vitamin C
 - Experimental
- Tunica albuginea incision
 - Alleviation of "compartment syndrome"-induced ischemia
 - Tunica vaginalis flap coverage

Figuerola et al, 2012; Moghimian et al, 2016

Testicular Torsion – Long-Term

- Pregnancy rates after testicular torsion
 - 90% for both salvage and orchiectomy groups
 - Pregnancy rate in general population 82 – 92%
 - No difference in mean time to pregnancy (approx. 7 months)

Gielchinsky et al, 2016

4. Transitional Urology



Transition - Background

- Purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from a pediatric (child-centered) to adult centered health care system
- Transfer of care from pediatric care providers to adult care providers as you get older

Transition - Background

- Taking care of adults is different than taking care of children
- Patients with spina bifida have increased medical needs than the general population and they need specialty care as adults

Brief History of Transition in the US

- **1984**- "Youth with Disability, The Transition Years"
- **1989**- Surgeon General "Growing up and Getting Medical Care: Youth with Special Health Care Needs"
- **1990**- Maternal and Child Health Bureau "Youth with Disabilities: A National Response"
- **2002**- AAP, AAFP & ACP Consensus Statement
 - 1) understand the rationale for transition
 - 2) have the knowledge and skills to facilitate that process
 - 3) know if, how, and when transfer of care is indicated

Brief History of Transition in the US

- **2007**-AAP Annual Leadership Forum "top-10 priority"
- **2011**-AAP recognized that widespread implementation had not been recognized
 - Pediatric providers were unclear on goals of transition
 - Limited availability of adult providers
- **2013**- "Current status of transition preparation among youth with special needs in the United States."
 - Less than 40% of individuals met transition core outcome measures
- **2014**- Got Transition™ (gottransition.org) and AAP Pediatric ECHO

Goals of Transition

- Encourage engagement in adult healthcare system
 - Prevent discontinuity of care: Over 60% of patients with spina bifida do not establish medical care once they leave pediatric care
 - Decrease morbidity: Use of Emergency Room is higher in young adults with chronic health conditions

Goals of Transition

- Maximize lifelong health and psychosocial needs
 - Diseases of adulthood need to be addressed: high blood pressure, diabetes, high cholesterol, obesity, cancer, osteoporosis
 - Psychosocial needs of adulthood need to be addressed: higher education, job placement, relationship goals, living arrangements

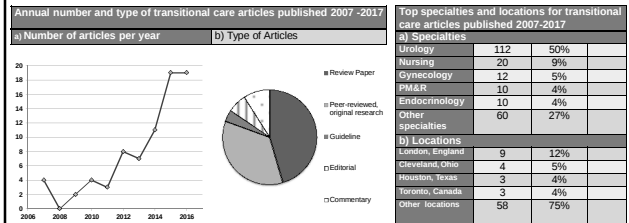
Goals of Transition

- Provide care that is coordinated and uninterrupted
 - Prevent delay in securing medical home: youth with chronic condition take twice as long to establish care with adult provider
 - Your health care providers need to communicate with your new doctors so medical information and history is passed along
 - Decrease dissatisfaction with medical care

Goals of Transition

- Improve not just health related outcomes as children become adults but also impact activities, social participation, environmental factors in order to help adults become fully functioning in society and contribute to society

Transition in Urology



Transition in Urology

Urologic Congenitalism

Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions: A Workshop Sponsored by the National Institute of Diabetes and Kidney Disorders

Michael H. Walsh, Hadley M. Wood, Dr. Veronica Gomez-Lobo, Taj R. Mattson, R. Kathleen J. Savin, Peter Scul, James E. Tamm, Evanston Northwestern Healthcare

Urologic Congenitalism

The Recommendations of the 2015 American Urological Association Working Group on Genitourinary Congenitalism

Jairam R. Eswara, Stephanie Kiehl, Martin A. Koyle, Dan Wood, and Hadley M. Wood

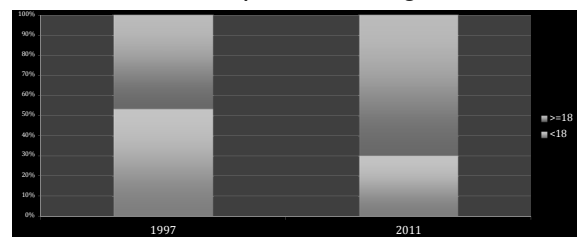
Transition – Urological Conditions

- Spina Bifida
- BEEC
- Hypospadias
- DSD
- Stones
- Cloaca Anomalies
- PUV/Renal Transplant
- VUR
- Pediatric cancer survivors
- Infertility/varicocele

Spina Bifida

- Most common birth defect in United States
- No longer a “childhood” disease
– >85% living into adulthood
- Requires LIFELONG care by specialty doctors

SB Hospital Discharges



Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS) 1997-2011, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual States and provided to AHRQ by the States.

Current Thoughts on Transition

- **“Current opinions regarding care of the mature pediatric urology patient”** Szymanski KM, et al. JPU. 2015
 - Survey of pediatric urologists (30% response rate)
 - **68%** of pediatric urologists also cared for the adult complex patients
 - Only **6.5%** of **pediatric urologists** felt adult complex patients should be cared for by adult general urologists
 - **80%** felt adult complex patients should be cared for by pediatric or adult urologist with an interest in adolescent/transitional urology
 - **69%** would refer to the adult urologist with an interest in complex patients
 - Only **45%** of the pediatric urologists had an interested adult urologist in their practice

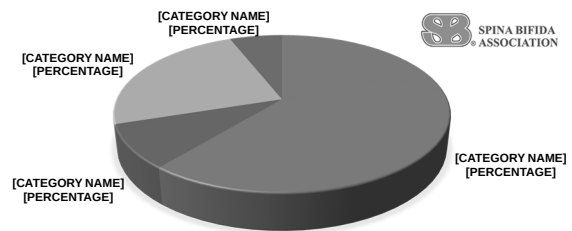
Current Thoughts on Transition

- **“Caring for urologic transition patients: Current practice patterns and opinions”** Zillioux JM JPU 2018
 - Survey of pediatric urologists from SPU (53% response rate)
 - **36%** had formal transition clinic
 - **64%** felt that adult complex patients should be cared for by specialized adult providers
 - **54%** of the formalized clinics were staffed primarily by PEDIATRIC providers
 - If staffed by adult urologist majority were reconstructive urologists (58%), then female and neurology (12%)

Current Thoughts on Transition

- **AUA Congenitalism Working Group 2016**
 - 60% Pediatric urologists
 - 12% Reconstructive urologists
 - 10% Female Pelvic Medicine urologists
 - 1% General adult urologists
 - 17% Other (fellows, residents, researchers, extenders)

Reality of Transition



Current Models of Transition

- Effective transition policy
- Implement transition tracking (registry)
- Assessment of transition readiness
- Transition planning
- Transfer to adult care/Adult approach
- Completion transfer/Ongoing care

Process of Transition

- Getting ready for adult health care
 - Start discussing in early adolescence
- Achieving independence for managing medical needs
 - Promote self management and health maintenance transition from parent or caregiver to the adolescent
- Assessment of readiness for transition
 - Review goals of transition
- Transfer to adult health care model

Recommended Health Care Transition Timeline

AGE:	12	14	16	18	18-22	23-26
	Make youth and family aware of transition policy	Initiate health care transition planning	Prepare youth and parents for adult model of care and discuss transfer	Transition to adult model of care	Transfer care to adult medical home and/or specialists with transfer package	Integrate young adults into adult care

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Transition Readiness Assessment Questionnaire (TRAQ)

Directions to Youth and Young Adults: Please check the box that best describes your skill level in the following areas that are important for transition to adult health care. There is no right or wrong answer and your answers will remain confidential and private.

Directions to Caregivers/Parents: If your youth or young adult is unable to complete the tasks below on their own, please check the box that best describes your skill level. Check here if you are a parent/caregiver completing this form.

	No, I do not know how	No, but I want to learn	No, but I am learning to do this	Yes, I have started doing this	Yes, I always do this when I need to
Managing Medications					
1. Do you fill a prescription if you need to?					
2. Do you know what to do if you are having a bad reaction to your medications?					
3. Do you take medications correctly and on your own?					
4. Do you reorder medications before they run out?					
Appointment Keeping					
5. Do you call the doctor's office to make an appointment?					
C. Do you follow up on any referral from health care provider?					

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Transfer to adult health care model

- Meet with pediatric specialist and adult specialist at the same time to transfer care
- Pediatric specialists may have appointments in the adult hospital
- Referrals are made to adult providers
- Medical records are organized and transferred with patient vs. shared EMR

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Transition - Barriers and Challenges

- Willingness of families and patients to transfer care
- Discomfort with the adult hospital
- Familiarity with pediatric hospital
- Insurance issues (ACOs)
- Privileges in the OR for both pediatric and adult providers

Transition - Barriers and Challenges

- **“How successful is the transition to adult urology care in spina bifida? A single center 7-year experience”** Szymanski KM, et al. JPU. 2017
 - Well established Transition Urology Clinic
 - Only **40%** (31/77) successfully transitioned
 - Only **half of patients with augments transitioned (20/41)**

Transition - Future/Research

- **“Caring for Adults with Congenital Genitourinary Anomalies: Adult Urology Department Leaders’ Perspectives on Programmatic Change”**
 - Qualitative study (Varda BK et al.)
 - **Perceived role** of adult programs in caring for aging patients with CGA
 - Considerations for **developing comprehensive care models** for this population in the adult setting.

감사합니다 Natick
Danke Ευχαριστίες Dalu
Thank You Köszönöm
Tack
Спасибо Dank Gracies
谢谢 Merci See
ありがとう

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